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NODULOULCERATIVE GRANULOMA OF THE LEGS

Treatment with Tocopherols

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A CASE of granuloma of the legs, with lipoidal changes compatible with a diagnosis of necrobiosis lipoidica diabeticorum, is reported because of the rapid response to treatment with preparations of vitamin E, together with histologic studies of changes in the course of treatment.

REPORT OF A CASE

Mrs. C., aged 52, in whom diabetes was first discovered in 1941, appeared in the clinic in 1942, with nodular lesions in both legs, at which time a diagnosis of erythema induratum, of the Phillipson type, was made. Rest and supportive treatment resulted in partial cure, with, however, a relapse in 1943, when ulceration occurred on the anterior aspect of the left shin. Exacerbations occurred from this time on, with involvement of both legs. She was obese.

In September 1946, there were multiple ulcerative lesions on the lower third of both shins, associated with pain and tenderness. No deep nodose lesions were felt, but there was thickening, with peripheral inflammation and some telangiectasia.

The diabetes was moderate, and the patient had an elevated level of sugar in the blood. She adhered to her diet at intervals and at times had treatment with insulin. Cholesterol determinations in five years varied from 0.159 to 0.208 mg. per hundred cubic centimeters.

In October she was admitted to the hospital for further studies. Following two biopsies a diagnosis of necrobiosis lipoidica diabeticorum was made. Previous treatment had been of little value, and rest in bed for three weeks had not resulted in any obvious change. On discharge she returned to work, which involved a good deal of standing, and she was given daily intramuscular injections of a preparation of vitamin E ("natopherol in oil" [1]), 250 mg., from December 2

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1. Abbott Laboratories supplied the preparations of vitamin E ("natopherol in oil," alpha, delta and gamma tocopherols, 250 mg. per cubic centimeter, equivalent to 200 mg. of alpha tocopherol, in standardization for injection purposes, and "natopherol," 50 mg. capsules of concentrate of natural alpha and gamma tocopherols obtained from vegetable oils by distillation).

to December 11. In all, 2,500 mg. of tocopherols were given. Improvement was noted after one week, when pain and tenderness began to disappear; healing of the ulcerative areas was evident, together with a decided diminution of the inflammatory reaction. As healing occurred, the areas became slightly yellow, smooth and atrophic, with telangiectatic vessels becoming more evident. Since daily injections in the hips became to painful, they were discontinued. Following this a vitamin E preparation ("natopherol" [1]), 100 mg. daily, was given by mouth.

One month later, healing had occurred. There was residual erythema, with atrophy and telangiectasia, but no thickening was evident. A third biopsy was done at this time. Treatment with tocopherols, 100 mg. daily by mouth, was continued, and on April 15 the area was represented by a residual atrophic scar, at which time a fourth, and final, biopsy was made.

Fig. 1.—Photograph of the legs of the patient before treatment (June 12, 1946).

Histologic Studies.—Biopsy No. 1 (October 16): The section consisted of skin and subcutaneous tissue, down to and including a strip of fascial tissue. The epidermis was intact; the papillae were decidedly flattened out and were represented by only a few shallow indentations of the epidermis. The epidermis was 8 or 9 cell layers thick. The stratum granulosum was thin, and there was a thin overlay of keratin. The papillary zone of the corium was thickened, and in it the capillary plexus was prominent; many of the vessels were somewhat dilated, and their endothelium showed decided hypertrophy. About many of the vessels there was a mild infiltration of the lymphocytes and plasma cells. The reticular layer of the corium extended down to the fascia, and there were a few islands of fat included in the deep margin. The incorporated islands of fat showed at their margins fairly intense infiltration with lymphocytes and plasma cells. The collagen in this zone was well preserved. Throughout the reticular zone of the corium there were extensive areas of necrosis of the collagen. The necrosis involved generally a linear area parallel with the surface, about the

center of the reticular zone, encompassing about half of this zone. At one point, however, the necrosis extended almost to the deep margin of the reticularis. The necrosis took the form of a swelling of the collagen bundles, producing compactness and apparent fusing of bundles. However, the fine fibrillar structure of the collagen could still be seen. There was no actual dissolution or liquefaction. The cells in the area were scant and showed evidence of degeneration, in that the cytoplasm could not be identified, the nuclei were shrunken, irregular and pyknotic, and some of them were fragmented, i.e., karyorrhexis was evident. With the trichrome routine stain (hematoxylin, phloxine and crocus), the degenerated collagen generally stained pink with the phloxine but still retained a faint yellow stain of some of the fibrils from the crocus. The general appearance of the degenerated areas was that of necrosis of cells and swelling of the

Fig. 2.—Biopsy no. 1 (October, 1946). Low power photomicrograph, showing necrobiosis and granulomatous changes in the corium.

collagen by imbibition of some phloxinophilic coagulum without actual dissolution. Along the upper and lower margins of the necrotic zone there was decided proliferation of connective tissue cells, with increased collagen content, and scattered through this reactive tissue and beyond it there were numerous tubercle-like structures, consisting of epithelioid cells and multinucleated giant cells. Some of these giant cells had a homogeneous center and peripherally distributed nuclei resembling closely the Langhans type, and in others the nuclei were bunched irregularly. Fat stains were not made.

Biopsy No. 2 (October 30): In general this section was similar to the first, but here the necrosis involved only one half of the longitudinal diameter of the section. At the margin of the necrotic zone in the granulomatous tissue were two arteries which show decided subintimal phloxinophilic swelling, causing thickening of the wall. The muscle cells were still distinct. The lumens were patent, and the lining endothelium appeared normal.

Scarlet red showed general pale pink staining of the swollen collagen bundles and between the bundles a scattering of fine and coarse lipid particles, some of which appeared free and some confined within cells. The latter state was

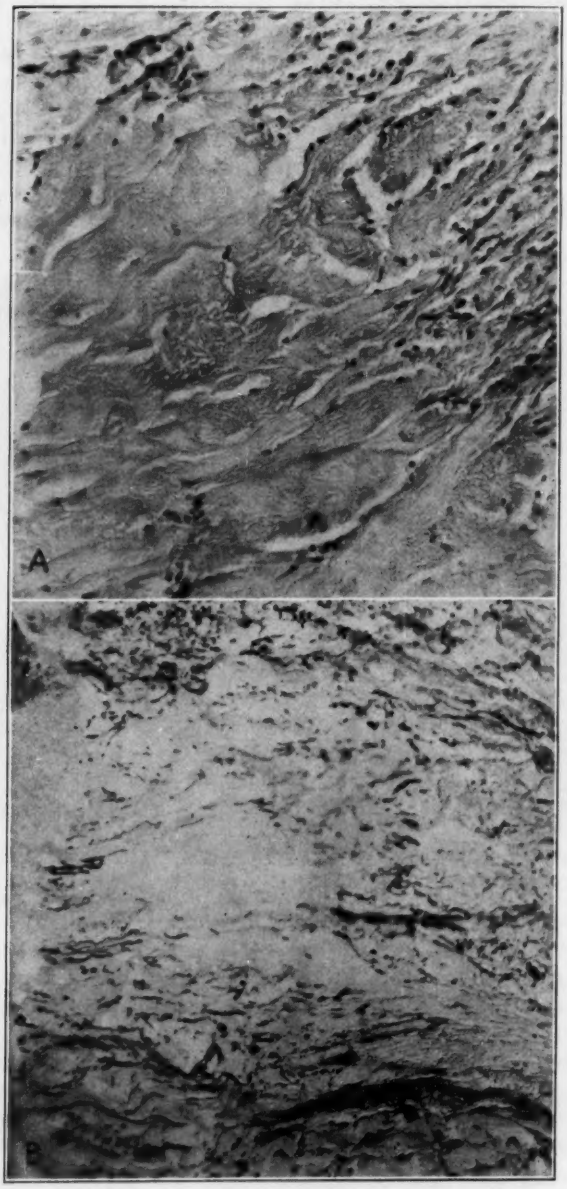

Fig. 3.—Biopsy no. 1. *A*, high power photomicrograph, showing an area of necrobiosis. *B*, elastic tissue stain of the corium shows loss of elastica in the necrobiotic zones.

particularly apparent along the margin of the fibroblastic reaction about the necrotic zone.

Elastic Tissue Stains in Biopsy Specimens No. 1 and No. 2: In the necrobiotic areas, in the center of some of the zones, the elastica had entirely disappeared. In others scattered fragments remained. Toward the periphery of the zones, there

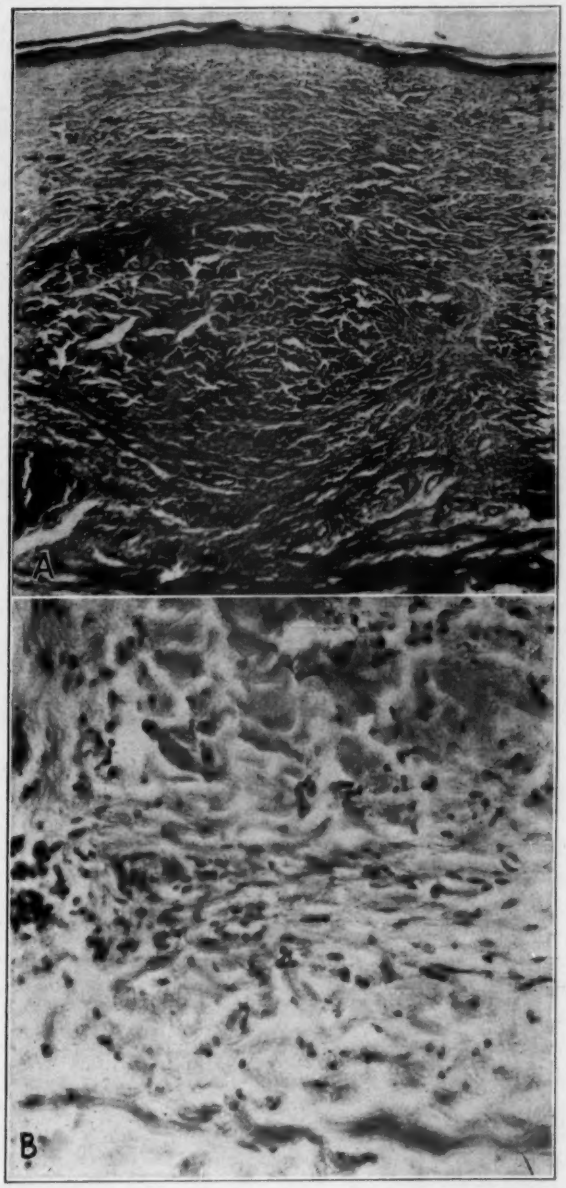

Fig. 4.—Biopsy no. 3 (January 1947). *A*, low power photomicrograph, showing decided reduction of necrobiosis and scanty granulomatous reaction. *B*, high power photomicrograph, showing only slight swelling of collagen, below which there is a zone of fibroblastic proliferation and only scant perivascular lymphocytic infiltration.

was an abundance of elastica squeezed between the swollen collagen bundles. Elsewhere the elastica appeared normal except for the disturbance in distribution caused by the granulomatous foci. There was a subepithelial zone, varying in thickness and apparently corresponding to the papillary zone of the corium, which was devoid of elastic fibers.

Biopsy No. 3 (Jan. 9, 1947): The epidermis and the zone papillaris were similar to those in the previous section, but in the papillaris there was only a mild diffuse lymphocytic infiltration and a few dilated capillary vessels. Extending through the corium and into the superficial fat about the vessels and sweat gland ducts, there was a patchy accumulation of lymphocytes, with a few plasma cells extending into the surrounding collagen and two small tubercle-like structures, one about the center of the corium and one near the deep margin.

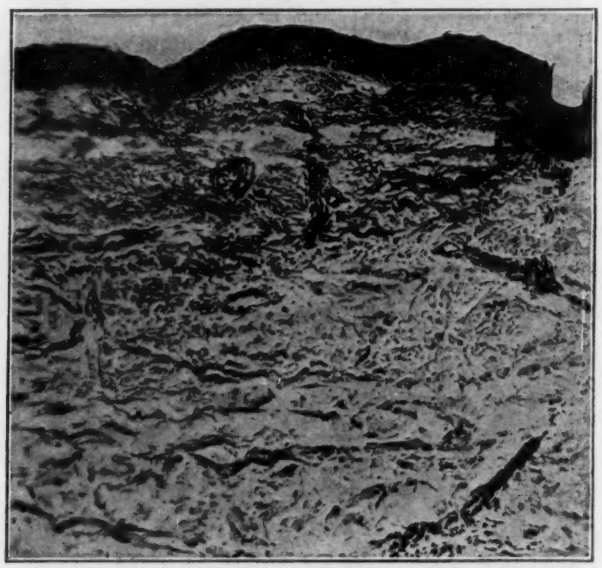

Fig 5.—Biopsy no. 4 (April 1947). Low power photomicrograph, showing nearly complete restitution of the corium.

Running through the center of the reticularis there was a zone of irregularly swollen collagen bundles, but not nearly so evident as in the two previous specimens. Between the collagen bundles there were fairly numerous well preserved spindle cells.

Scarlet red stains showed only a few mononuclear cells containing lipid droplets and here and there free minute fat droplets in small numbers. There appeared to be some residual collagen swelling, only moderate granulomatous reaction and scarcely any lipid.

Elastic tissue stains. In a few small areas, the elastica was absent and the collagen appeared more fibrillary. Generally there was an abundance of elastica. There was a subepithelial zone, varying in thickness and apparently corresponding to the papillary zone of the corium, which was devoid of elastic fibers.

Biopsy No. 4 (April 15): The section consisted of skin and a small amount of subcutaneous fat. The surface of the epidermis was intact and smooth. All

portions of the epidermis were atrophic, the stratum granulosum was only 1 cell layer thick and the rete malpighii 6 to 7 cells in depth. There was a total loss of rete pegs and dermal papillae, the dermoepidermal junction being marked

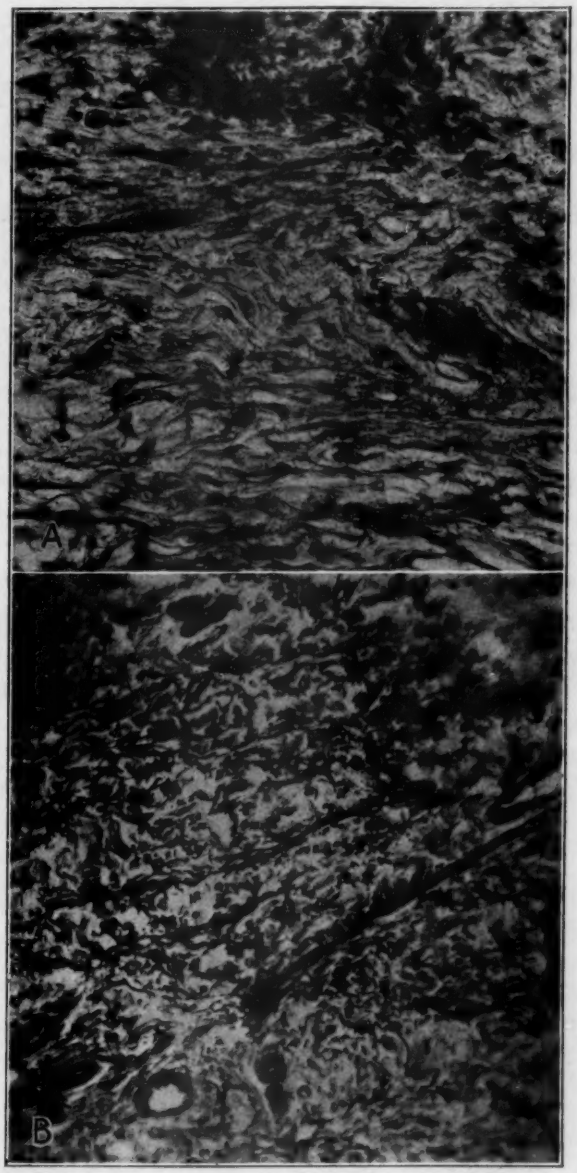

Fig. 6.—Biopsy no. 4. *A*, high power photomicrograph of the corium, with no evidence of necrobiosis, and reconstituted cellular fibrillary collagen. *B*, elastic tissue stain of the corium, showing reconstitution of the elastica.

by a slightly undulating line. There was no tubercle formation and no evident necrobiosis as described in the previous biopsies. The reticularis was composed

of closely meshed small collagen bundles, between which there were well preserved spindle cells. In the reticularis there were a few slightly dilated arterioles, about some of which there was a mild lymphocytic infiltration. Scharlach R stains showed no lipids.

The gross granulomatous process had disappeared, leaving only slight lymphocytic perivascular infiltration, and there was no evident necrobiosis.

Elastic tissue stain. There was a diffuse distribution of elastica, which was mostly that of normal skin. However, at one end of the section the elastica was fragmented, and in a zone near the deep margin there was a dense feltwork of fine elastic fibrils in excess of normal. There was a subepithelial zone, varying in thickness and apparently corresponding to the papillary zone of the corium, which was devoid of elastic fibers.

COMMENT

This case of noduloulcerative granuloma of the legs, associated with necrobiotic changes together with lipid deposition, is reported because of the response of the disease to vitamin E therapy.

In this case, three histologic changes occurred as a result of treatment, practically all interdependent. There was rehabilitation of the collagen fibers, which was coincident with two other observations, namely, the disappearance of the granulomatous reaction and the lipoidal depositions. That these changes were brought about by treatment with vitamin E preparations cannot be doubted.

It might be pertinent to state that in a paper on necrobiosis lipoidica diabeticorum, Zeisler and Caro [2] pointed out that apparently a deposition or imbibition of lipids develops in the necrobiotic intercellular tissue. Michaelson and Lane [3] concluded that the disease is more closely related to gangrenous processes than to any other integumentary process and advanced the view that lipoidal deposits are superadded to this change. It would therefore seem that most probably the disappearance of lipid deposits is of secondary importance. In this connection, frequent determinations of cholesterol in the blood following treatment with tocopherols in this patient and other patients revealed no significant alteration in their values. Furthermore, ulceronodular granuloma of the legs, without lipoidal change and with a histologic diagnosis of erythema induratum, responded in similar fashion to injections of tocopherols after failing to respond to other methods of treatment over a long period of time. Rehabilitation of the collagenous system together with its ground substance is probably fundamental to this change.

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2. Zeisler, E. P., and Caro, M. R.: Necrobiosis Lipoidica Diabeticorum, Arch. Dermat. & Syph. **30**:796 (Dec.) 1934.

3. Michaelson, H. E., and Lane, C. W.: Necrobiosis Lipoidica Diabeticorum (Urbach): Dermatitis Atrophicans Lipoides Diabetica (Oppenheim), J.A.M.A. **103**:163 (July 21) 1934.

SUMMARY

A case of noduloulcerative granuloma of the legs, histologically consistent with necrobiosis lipoidica diabeticorum, is reported because of the rapid response to treatment with injections of a vitamin E preparation. An evaluation is also made of the histologic changes resulting from treatment.

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ABSTRACT OF DISCUSSION

DR. FRED D. WEIDMAN, Philadelphia: There are two ways of regarding this disease. First, there is the question whether the lipids are the primary agency, that is, according to the theory of Urbach that the disease is one of the lipoidoses, a matter of autonomous fault within the tissue. Second, the fat may be present as a secondary development. Thus, it is axiomatic in pathology that dead tissue in general is subject to secondary fatty degeneration.

It has gradually become the consensus that the second theory is the correct one, particularly in view of the regularity, almost invariability (Dr. Laymon will bring that out more thoroughly at this meeting), with which there are vascular changes of the order of sclerosis; then, with the impairment of nutrition of the part, necrobiosis takes place and then fatty degeneration. This is the course of events which parallels that of anemic infarction, such as seen in the heart, kidney and spleen. For example, an anemic infarct is yellow to the naked eye, due partly to hemosiderin pigment, and partly to fatty degeneration. The centers of old tubercles are yellow because of fatty degeneration and perhaps not at all because of anything inherently faulty in the lipid metabolism.

Perhaps the study presented gives evidence in the other direction. It is difficult to understand how vitamin E should play such a profound part in altering the sclerotic changes and that there should be restitution from these fatty changes, but it would appear that vitamin E induces a change in the metabolism of the cells whereby they return to their original normal metabolic state.

However, perhaps one objection to that thesis may be made without eliminating the theory of arteriosclerosis as the primary factor concerned, namely, that vitamin E acts on tissue which is already on the way to recovery, that is, old tissue which ordinarily, in the absence of vitamin E, for example, would require a longer or shorter time to return to normal, and the effect of the vitamin E is simply to augment the normal processes of repair. Perhaps the answer to this lies in testing the action of vitamin E in other necrobiotic conditions that are not classifiable among the "dyslipoidoses," such as granuloma annulare, and in which the morbid microscopic changes so closely parallel those in necrobiosis lipoidica diabeticorum.

Perhaps Dr. Burgess and Dr. Pritchard have suggested the use of tocopherols in other diseases in which tissues have low biologic activity, such as morphea and scleroderma, and perhaps for collagenous tissue in general.

DR. NELSON PAUL ANDERSON, Los Angeles: I would like to congratulate Dr. Burgess and Dr. Pritchard, because I think that they have made a fundamental observation. I would like to know what suggested their use of vitamin E in this particular instance. Preparations of vitamin E have been used a great deal in my own family, in the treatment for fibrositis. There seems to be something fundamental taking place as regards collagenous tissue. It is known that pads occur on the backs of the fingers, so-called knuckle pads, which in many instances are

associated with Dupuytren's contracture of the palms and fibrositis elsewhere. While Dupuytren's contracture is primarily considered a surgical condition and is usually operated on, it does respond to treatment with tocopherols. There is an article by C. L. Steinberg of Rochester, N. Y. (*M. Clin. North America* **30**:221 [Jan.] 1946), in which he recommends treatment with tocopherols for Dupuytren's contracture.

I have not thought of the part played by vitamin E in granuloma annulare or necrobiosis lipoidica diabeticorum.

Vitamin E has a third effect, namely, it can act as an estrogen so that tocopherols can be given to persons who cannot tolerate ordinary estrogenic substances.

There seems to be a relationship between the effects of this type of treatment and the effects from estrogenic and androgenic substances on metabolism and photosensitivity.

I think that there is something fundamental about this observation with respect to disorders of collagenous tissue. These changes have been regarded as irreversible, but Dr. Burgess and Dr. Pritchard show that they are not irreversible.

Dr. Carroll S. Wright, Philadelphia: I think that there may be one other action that ought to be mentioned, that is, vitamin E is supposed to promote the development of vitamin A.

Vitamin A has been used as cod liver oil ointment. It is probably the vitamin A in the cod liver oil that does good, and that might be a factor in this particular case.

Dr. Francis A. Ellis, Baltimore: I should like to call attention to the observation that spontaneous cure sometimes occurs in granuloma annulare, especially following biopsy, and may occur in necrobiosis lipoidica diabeticorum following ulceration.

Dr. J. Frederick Burgess: I wish to thank all those who took part in the discussion. I had been making some observations in certain dermatoses in the past year of the effects of vitamin E, and I had come to the conclusion that possibly vitamin E had some effect on fat metabolism. That was only one of the reasons that it was used in this case. I am inclined to think that this may have been a false premise.

That vitamin E has a more specific effect on collagenous tissue is evidenced by some effects in a series of cases of lupus erythematosus which are to be published. All patients treated have shown improvement within a short time, and more superficial nonthickened lesions have cleared up in somewhat dramatic fashion.

Further detailed metabolic and histologic studies are in progress in order to shed further light on the functions of the tocopherols in human beings.

CONGENITAL ICHTHYOSIFORM ERYTHRODERMA

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CONGENITAL ichthyosiform erythroderma was described by Brocq [1] in 1902 after the prolonged observation of several patients in whom the disease was characterized by diffuse redness beginning at birth, a shiny appearance of the face and widespread hyperkeratosis resembling ichthyosis. The first and most important consideration of the subject in the English literature was by MacKee and Rosen,[2] whose important monograph was published in 1917. These authors completely reviewed the literature on the subject and presented the history of the disease and a detailed discussion of the clinical and histologic features. MacKee and Rosen also discussed the nosologic position of congenital ichthyosiform erythroderma, especially regarding its relationship to ordinary ichthyosis. These authors found that up to 1917 a total of 45 cases of the disease had been reported.

In 1925 Weiss and Tobias [3] reviewed the literature from 1917. They found 10 additional cases and reported 6 of their own. Since that time other notable contributions have been made by Goeckerman (1926),[4] MacLeod (1928),[5] Goldsmith (1928),[6] Williamson (1934)[7] and Lawless (1941).[8]

From the Division of Dermatology, University of Minnesota, H. E. Michelson, M.D., Director.

1. Brocq, L.: Érythrodermie congénitale itchthyosiforme avec hyperépidermotrophie, Ann. de dermat. et syph. **3**:1-31, 1902.

2. MacKee, G. M., and Rosen, I.: Érythrodermie Congénitale Ichthyosiforme, J. Cutan. Dis. **35**:235-251, 343-361 and 511-540, 1917.

3. Weiss, R., and Tobias, N.: Congenital Ichthyosiform Erythroderma, Arch. Dermat. & Syph. **12**:182-194 (Aug.) 1925.

4. Goeckerman, W.: Bullous Ichthyosiform Erythroderma, Arch. Dermat. & Syph. **14**:158-172 (Aug.) 1926.

5. MacLeod, J. M. H.: Note on Two Cases of Ichthyosis Bullosa, Brit. J. Dermat. **40**:51-58, 1928.

6. Goldsmith, W. N.: Congenital Keratoses with Bullae, Brit. J. Dermat. **40**:59-77, 1928.

7. Williamson, G. R.: Congenital Ichthyosis, J. Pediat. **5**:484-490, 1934.

8. Lawless, T. K.: Congenital Ichthyosiform Erythroderma, Arch. Dermat. & Syph. **44**:30-36 (July) 1941.

Brocq observed his first case in 1881. Vidal and Hillairet had studied the patient and had considered seborrhea, with ichthyosis and pityriasis rubra pilaris, as diagnostic possibilities. Later, Vidal, after a more careful study, changed his mind and presented the case before the Société de biologie, in April 1882, under the title of hyperépidermotrophie généralisée. Brocq thought that the dermatosis suggested ichthyosis in a general way, but differed from the latter in many particulars. In the next few years he collected a number of cases, some of which had been already reported by other observers under various titles. As a result of careful study of these cases he became convinced that he was dealing with a new clinical entity of which there were several varieties. He gave the disease the name of érythrodermie congénital avec hyperépidermotrophie. Later, after he had ascertained that there were cases not associated with rapidly growing hairs and nails, the title ended with: "avec ou sans hyperépidermotrophie." Finally, after he had encountered and recognized a bullous type, the caption was lengthened to "érythrodermie congénital ichthyosiforme avec ou sans hyperépidermotrophie et avec ou sans bulles." After Brocq's publication in 1902, articles were published by Thibierge, Rasch, Danlos, Jadassohn, Pizard, Langevin, Nicolas and Jambon, Darier and several others. Many of the authors agreed with Brocq, and others were not in accord with his views, especially as to classification.

According to Bruhns[9] the first case of congenital ichthyosiform erythroderma was reported by Sangster in 1895 under the title of "A Case of Congenital Exfoliation," and the second case was reported by Rasch as erythrodermie exfoliativa universalis congenita familiaris. In 1903 Rille, without knowledge of Brocq's publication, described a dermatosis which he called keratosis rubra congenita, which, he expressed the belief, was closely related to ichthyosis vulgaris. Rille's description of this disease coincides with the present concept of congenital ichthyosiform erythroderma.

CLINICAL FEATURES

Congenital ichthyosiform erythroderma ordinarily begins at birth or shortly thereafter, although in a few instances it has been reported as beginning in late childhood or adult life. It occurs equally in both sexes and heredity does not seem to play an important role. Erythroderma and keratosis are the chief characteristics, the latter being concomitant with the former or preceding it. Although the keratosis is oftenest generalized, it may vary considerably in severity and extent. In some cases, thick horny plates form or warty excrescences may be present, as in ichthyosis hystrix. In some cases the skin is diffusely red, while in others it may be dark gray, brown or almost black, simu-

9. Bruhns, C.: Ichthyosis, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 8, pt. 2, pp. 1-52.

lating acanthosis nigricans. The axillas, cubital and popliteal spaces, body folds, palms and soles are the areas most intensely involved. These locations stand in direct contrast to those which are most affected in ordinary ichthyosis. Series of elevated hyperkeratotic nodules may form, or thick dry scaly plaques may be present. On the palms and soles there may be enormous masses of yellow or amber horny material, most frequently resembling ordinary calluses, although in some cases the lesions may be warty, resembling arsenical keratoses. Deep fissures may be present. The formation of horny plates is frequently pronounced on the sides and back of the neck and the umbilical region, and in these areas the cutaneous markings may be greatly exaggerated. In some cases there is much scaling, especially over the body folds.

Erythema and erythroderma are particularly noticeable on the neck, folds, extremities, face, chest and abdomen, and in some cases the disease may resemble pityriasis rubra pilaris or pemphigus foliaceus. The redness is especially noticeable following removal of the scales. As a rule the face is especially red, smooth, brilliant and shiny, as if the skin were coated with collodion. Ectropion of moderate degree may be present. In some cases redness of the skin may be almost entirely lacking, which caused Blum [10] to state that he preferred the term hyperkeratose ichthyosiforme to erythrodermie ichthyosiforme.

The nails are sometimes thickened and show subungual masses of keratotic material. There may also be transverse or longitudinal striations and stippling, as in psoriasis. In some patients with ichthyosiform erythroderma the nails grow two or three times faster than in normal persons. The hair may also grow rapidly and develop excessively. Speedy growth of hair and nails, however, is not a constant clinical sign.

Hyperhidrosis of the palms and soles is a frequent observation and may be so severe that the epidermis becomes macerated. Facial hyperhidrosis may also be present, although in most cases it is the sebaceous secretion which is augmented. As a rule there is heavy scaling of the scalp, which may be either dry or oily.

Bullae may or may not be present in ichthyosiform erythroderma. They may form spontaneously or after trauma, especially on the neck and legs. They usually occur in crops and as a rule are asymptomatic. Bullae appear more frequently in younger persons, and as the patient grows older they tend to cease forming. An outcrop of bullae may be accompanied with slight fever. In most cases the bullae rupture quickly and become covered by horny masses. Lenglet, Darier and Goeckerman [11] suggested that there might be a relationship between ichthyosiform erythroderma and epidermolysis bullosa. Weiss and Tobias [8]

10. Blum, P.: Érythrodermie congénitale ichthyosiforme on hyperkératose ichthyosiforme, in Darier, J., and others: Nouvelle pratique dermatologique, Paris, Masson & Cie, 1936, vol. 6, p. 332.

11. Cited by Bruhns.[9]

stated the belief that there should be no differentiation between the wet and dry types of ichthyosiform erythroderma and that the former represented superimposed bullous impetigo. They, too, mentioned the relationship to epidermolysis bullosa. Goldsmith stated that the bullae in ichthyosiform erythroderma were partly infectious and partly traumatic. MacKee and Rosen [2] noted that bullae were present in 27 per cent of 45 cases.

Most patients with ichthyosiform erythroderma remain well physically and mentally, although dental abnormalities or anomalies of the ears may be associated with cutaneous changes. Blum [10] mentioned that the mucous membranes may be involved and that in some cases there might be cutaneous atrophy or a pseudoscleroderma tous appearance of the skin.

Ichthyosiform erythroderma is usually generalized and symmetric, although circumscribed types have been described occurring as a rule on either the upper or the lower extremities. In certain instances this form is represented by localized warty excrescences simulating verrucous nevus. Certain observers have expressed the belief that palmar and plantar keratoses and mal de Meleda represent a circumscribed form of ichthyosiform erythroderma.

Except for minor exacerbations it remains fairly fixed, although in some cases its severity is lessened in older persons, especially as far as cessation of bullae and diminution of erythroderma are concerned. There have been no reports of complete permanent recovery. The pathogenesis and causation are extremely obscure.

HISTOLOGIC FEATURES

The histologic observations in ichthyosiform erythroderma are well defined. Extreme hyperkeratosis is a striking feature. There is frequently hypertrophy of the granular layer, although in some areas it is absent. The stratum mucosum is apt to be thicker than is normal. The entire epidermis is acanthotic, the papillary bodies being elongated, irregular and papillomatous. There are no microabscesses or infiltrate in the epidermis as in psoriasis.

Changes in the cutis are not striking. There may be some edema and moderate perivascular infiltration, especially in the papillary bodies. The sweat and sebaceous glands are most likely to be overdeveloped. There are usually no changes in the elastic tissue, although in some cases fragmentation and diminution of these fibers have been described.

DIFFERENTIAL DIAGNOSIS

There are several cutaneous diseases which may more or less resemble congenital ichthyosiform erythroderma. In most instances the differentiation from psoriasis is not difficult. The presence of psoriasis at birth is almost unheard of, whereas it is the rule in ichthyosiform erythro-

derma. Psoriasis is rarely as generalized as ichthyosiform erythroderma, and between the lesions of the former the skin is normal, while in the average case of ichthyosiform erythroderma it is difficult to find a single area of completely normal skin. Psoriasis does not remain as fixed as ichthyosiform erythroderma, and in the former bullae are always absent. Histologically the epidermal changes are different in the two diseases, ichthyosiform erythroderma having no epidermal infiltration or microabscesses.

Pityriasis rubra pilaris is likewise not congenital and does not begin as a generalized disease, as is the case in ichthyosiform erythroderma. Follicular papules, which are an important feature of pityriasis rubra pilaris, offer another important point of differentiation.

Points of Differentiation Between Ichthyosis Vulgaris and Ichthyosiform Erythroderma

Ichthyosis Vulgaris	Ichthyosiform Erythroderma
Appears at young age, not strictly congenital	Strictly congenital
Localization; folds, palms, soles spared	Palms, soles, folds most intensely involved
Moderate hyperkeratosis	Extreme hyperkeratosis, sometimes papillomatous
Adjacent skin normal	Skin more or less red
Absolute dryness, no seborrhea	Intense seborrhea
No overdevelopment of hair and nails	Rapid development of hair and nails
Fixed evolution	Progressive course
Histologic Differences	
Horny layer thick	Horny layer extremely thick
Granular layer sometimes diminished or absent	Granular layer usually hypertrophic
Stratum mucosum thin	Stratum mucosum thick
Papillary bodies underdeveloped	Papillary bodies long and irregular
Sweat glands and follicles involved (keratosis pilaris)	Overdevelopment of sweat and oil glands
Perivascular infiltrate	Inconstant perivascular infiltrate

Idiopathic erythroderma (pityriasis rubra) is not congenital and not as perennial as ichthyosiform erythroderma. There are no thick horny plates in the former as in the latter. In ichthyosiform erythroderma the general health is maintained, while in idiopathic erythroderma there are serious systemic disturbances.

Pemphigus foliaceus may superficially resemble ichthyosiform erythroderma. In the latter, however, the bullae are inconsistent and the health is unimpaired. Pemphigus foliaceus is not congenital and is far less hyperkeratotic than ichthyosiform erythroderma.

Ordinary verrucous nevi are more circumscribed and fixed than lesions in ichthyosiform erythroderma.

Differential diagnosis is more difficult in ichthyosiform erythroderma and ichthyosis vulgaris. Although the problem is not completely settled, most observers are willing to admit that they are two separate entities. The points of differentiation are briefly outlined in the accompanying table.

REPORT OF A CASE

History.—R. B., a white man aged 29, was born at term; the delivery was normal. Neither the father, mother, five sisters, one brother nor any other known relatives had a similar disease.

At birth the skin was diffusely red. Within the first few weeks of life the parents noted that the skin was abnormally dry and constantly peeling. No bullae were noted at any age. Besides measles and pertussis the general health had always been good. In 1941 the patient went to Los Angeles, and there was decided improvement for six months; then the disease recurred and was worse than ever. The patient perspired only on the palms and soles and was intolerant of heat, even though the disease improved somewhat in the summer. Various types of treatment were of practically no avail.

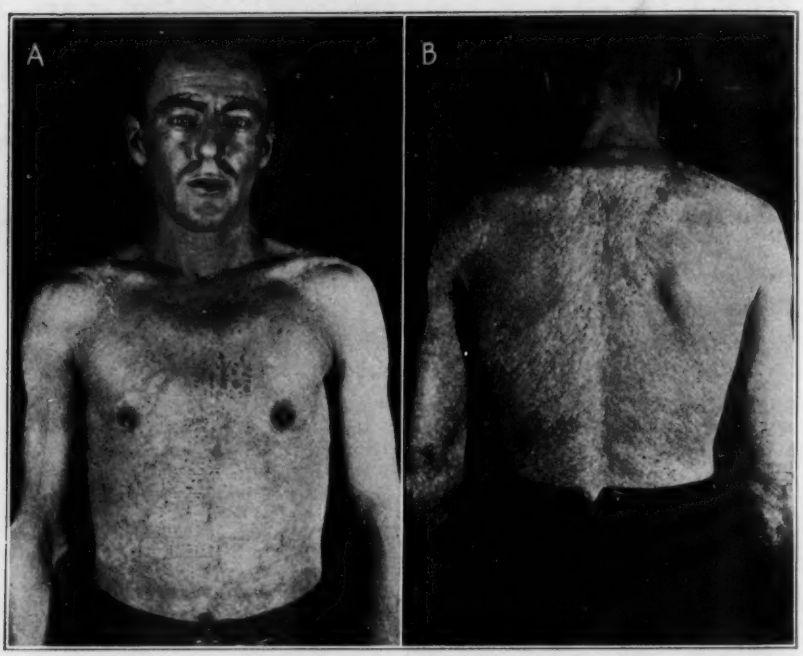

Fig. 1.—Congenital ichthyosiform erythroderma in the patient reported. *A*, shiny oil face and thick mortar-like plates on the chest, with generalized scaling and redness. *B*, lesions simulating inveterate psoriasis on the back.

Dermatologic Examination.—The hair was normal in amount and texture, and there were no dental abnormalities. The scalp was covered with heavy dry mortar-like scales. Similar scaling was present in the brows. The face was brightly erythematous, greasy and shiny. Practically the entire trunk was dry and scaly. The scales were much thicker on the upper part of the back, abdomen and distal parts of all the extremities. Here the scales resembled armor plate in some places, while in others the lesions simulated ordinary plaques of psoriasis. The knees and elbows were not especially affected; in fact, the maximum points of involvement were the cubital and popliteal spaces and body folds. The palms and soles were diffusely keratotic, as if they were covered by heavy callouses. The palms and soles were moist. All of the nails presented transverse ridging

and stippling. Some nails showed heavy deposits of horny material beneath them. No follicular papules were present as in pityriasis rubra pilaris. Physical examination showed no abnormalities other than the cutaneous ones.

Laboratory Examinations.—The patient was admitted to the University of Minnesota Hospital and thoroughly studied. Results in all laboratory studies were normal except the basal metabolic rate, which was + 29 per cent.

Histologic Examinations.—A biopsy specimen was obtained from a red scaly area on the upper portion of the back. The tissue was fixed in formaldehyde, embedded in paraffin and sectioned in the usual manner. Sections were stained with hematoxylin and eosin and by the Weigert and Van Gieson methods.

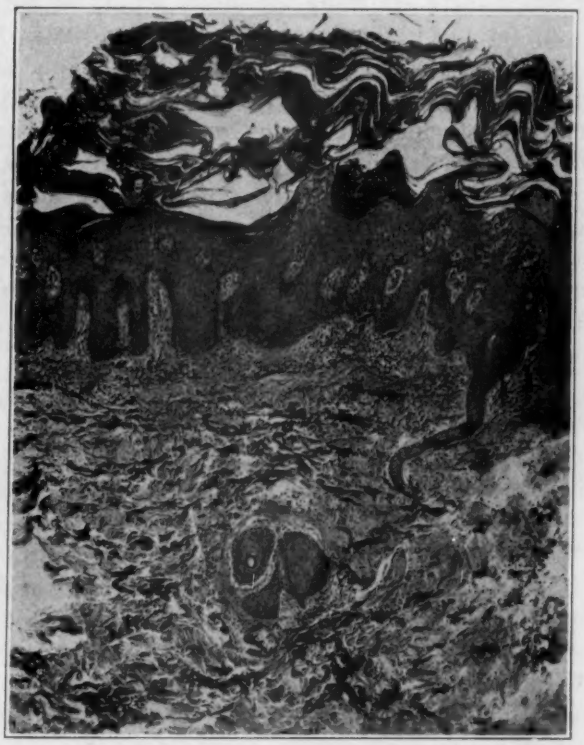

Fig. 2.—Photomicrograph of a section showing hyperkeratosis, granulosis and acanthosis of congenital ichthyosiform erythroderma, with only slight infiltration in the cutis.

Sections stained with hematoxylin and eosin showed excessive hyperkeratosis with some parakeratosis. There were a few scattered lymphocytes and polymorphonuclear leukocytes in two or three portions of the stratum corneum, although no actual microabscesses were noted. The thickness of the granular layer varied from a thinning in some areas to complete absence in others. There was irregular acanthosis of the entire epidermis and a moderate perivascular lymphocytic infiltrate in the upper portion of the cutis. No sebaceous glands were noted in the sections studied.

In sections stained by the Van Gieson method, the entire cutis assumed the characteristic red tint and the fibers appeared normal.

Sections stained by the Weigert method showed a mild degree of fragmentation of the elastic fibers.

COMMENT

The general term ichthyosis includes several abnormalities of cornification, which vary in extent and severity. Although there is general agreement as to the features characterizing most of the subdivisions of this group, there are some in which confusion still exists. Congenital ichthyosiform erythroderma is included in the latter category.

There seems to be universal agreement that ordinary ichthyosis vulgaris, of which there are many variations, should be differentiated from the severe form of ichthyosis congenita, also known as "harlequin fetus," ichthyosis fetalis or keratosis maligna diffusa. This rare disease is characterized by an intrauterine change of the fetal skin, and the child is usually born as a nonviable monstrosity. In some cases the child lives a few hours or a few days, but the entire skin is hyperkeratotic and deeply furrowed and resembles plates of armor. The lids, ears and lips may be missing, being replaced by horny folds giving the child the look of a mummy. Death soon results from inability to secure nutrition or from abnormalities in the development of the internal organs.

Riecke [12] expressed the belief that certain cases of congenital ichthyosis should be separated from the type previously described as ichthyosis congenita gravis. He discussed two less severe forms: One, in which the aforementioned changes were present at birth in a milder or partially developed manner, but instead of dying in a few days the infants lived, was termed ichthyosis congenita larvata. Bruhns described patients with ichthyosis congenita who survived for many years. In these cases the horny plates were much thinner and not as universally distributed as in the severe type. Riecke designated a third type as ichthyosis congenita tarda, in which there were no changes (or extremely mild ones) at birth, and only after days, weeks or even months changes developed which were identical to those in the second group.

Siemens [13] later suggested that Riecke's terminology be changed. He agreed that the true severe type should be designated ichthyosis congenita gravis, but felt that Riecke's second type (ichthyosis congenita larvata) should be called ichthyosis congenita mitis. He suggested the term ichthyosis congenita inversa for Riecke's term ichthyosis congenita tarda, since the latter word stands in opposition to the word congenita. The third type was differentiated from ordinary ichthyosis

12. Riecke, E.: Ueber Ichthyosis congenita, Arch. f. Dermat. u. Syph. **54**: 289-340, 1900.

13. Siemens, H. W.: Zur Differentialdiagnose und Prognose der überlebenden Fälle von Ichthyosis congenita, Arch. f. Dermat. u. Syph. **156**:624-655, 1928.

by its inverse localization, even though both appeared after birth. It is at this point that congenital ichthyosiform erythroderma comes into the discussion.

While Brocq expressed the opinion that ichthyosiform erythroderma should be clearly differentiated from ichthyosis vulgaris and the severe form of ichthyosis congenita, he admitted that it was difficult to decide whether or not the disease he described was an attenuated form of ichthyosis congenita. Later writers, especially Bruhns, stated the belief that ichthyosis congenita inversa (Siemens) and congenital ichthyosiform erythroderma were one and the same. The principal symptoms of Brocq's disease (onset at birth or shortly after, involvement of flexures, face, palms and soles) also characterize mild cases of ichthyosis congenita. The presence of redness and bullae are admittedly inconstant in ichthyosiform erythroderma and have been reported by Riecke and Siemens in the mild forms of ichthyosis congenita.

Similar comparisons have also been made regarding the rapid growth of hair and nails. It would thus seem that the cases described as mild types of ichthyosis congenita by Riecke and Siemens and Brocq's congenital ichthyosiform erythroderma have no clearcut points of clinical or histologic differentiation and must be regarded as identical. Regarding terminology, it would seem preferable to employ the term ichthyosis congenita mitis or inversa rather than erythroderma ichthyosiforme, since the latter places emphasis on the group of erythrodermas rather than ichthyosis, emphasis which in our opinion is not deserved.

The question of localized forms of ichthyosis is a difficult one and as yet not fully decided. It is not within the scope of this paper to discuss the classification of ichthyosis hystrix, palmar and plantar keratoses and verrucous nevi and their relationships to other anomalies of cornification. It would seem preferable from the standpoint of simplicity, however, especially until more is known about them, to classify these abnormalities of cornification under the broad heading of ichthyosis.

SUMMARY AND CONCLUSIONS

Congenital ichthyosiform erythroderma is a rare dermatosis, usually beginning at birth or shortly thereafter, characterized clinically by erythroderma and keratosis. The localization on folds and flexural surfaces is the opposite to that of ichthyosis vulgaris. Bullae may or may not be present. The disease is perennial, lasts a lifetime and does not impair the general health.

The chief histologic features are extreme hyperkeratosis, granulosis and acanthosis. Changes in the cutis are slight.

A case of ichthyosiform erythroderma in a white man aged 29 is reported.

In our opinion ichthyosiform erythroderma is identical with ichthyosis congenita of the mild type (ichthyosis congenita inversa, Siemens).

The term proposed by Siemens is preferable to congenital ichthyosiform erythroderma, since the latter emphasizes erythroderma rather than ichthyosis.

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MYCOSIS FUNGOIDES

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MYCOSIS fungoides is an uncommon disease as to the exact nature of which there is still considerable difference of opinion. The last review of the subject on a broad basis was in 1944, when Goldsmith [1] in a paper on reticuloses approached the subject from the clinical point of view, while Robb-Smith [2] discussed the pathologic aspects, emphasizing the need for study of material from all cases which became available. In view of the rarity of the disease and particularly of cases in which there was visceral involvement we feel justified in reporting on the following case.

REPORT OF A CASE

K. J. P., a clerk aged 36 years, was admitted to Crumpsall Hospital, Manchester, England, on July 7, 1945. He was in good health until June 1942, when he noticed an itching rash in the middle of the back, which subsequently spread all over the back and onto the face. Some time later several lumps (obviously enlarged lymph nodes) appeared in the neck and groins, the size of which varied in the months and years that followed. On July 11 he was admitted to a hospital in London. His eruption then appeared to be seborrheic dermatitis, which had cleared up when he left the hospital in July 1943. In January 1944 another eruption appeared on the face only. Treatment with different ointments and roentgen rays cleared the face, though he did not feel well and continued to lose weight. Early in 1945 he noticed a lump on the back and shortly afterward another one on the left knee. Subsequently more lumps appeared on the scalp, chest, back and limbs. Roentgen rays directed to the scalp caused the tumors there to melt away temporarily, while new tumors appeared in other places, gradually increasing in size and number.

On clinical examination (July 7) the patient looked emaciated. His face was sunken and his speech indistinct. He complained of over-all weakness and soreness. His mouth and throat in particular felt sore, causing him difficulty and pain in speaking and swallowing. There was no itching. The whole body surface was studded with tumors, varying in size from that of a split pea to that of a large tomato. They were freely movable and nowhere attached to the underlying tissues. The small ones were oval or rounded and only slightly raised;

1. Goldsmith, W. N.: Brit. J. Dermat. **56**:107, 1944.
2. Robb-Smith, A. H. T.: Brit. J. Dermat. **56**:151, 1944.

the large tumors were also sessile, prominent up to a height of 5 cm. and hemispherical or flat and their surface either smooth or lobulated. Some of them were umbilicated, others ulcerated in the center (fig. 1). The overlying skin varied from the bright red of a raw tomato to brownish red and dark brown; the consistency was firm or rubbery. The tumors were particularly numerous and aggregated on the back, elbows, thighs and knees, less numerous on the scalp, chest and abdomen and absent on the palms and soles. Lesions of a different type were present mainly on the chest and abdomen, but also on the face, back and limbs. These were slightly elevated plaques, varying in size from 1 to 8 cm. in diameter. They were more or less irregular, though fairly well defined in outline, and brownish red. The tongue was bulky and indurated, the gums swollen and the hard and soft palate infiltrated and ulcerated. The cervical, submental, axillary and inguinal glands were considerably enlarged, the latter reaching the size of a duck's egg. They also were of a rubbery consistency, freely movable

Fig. 1.—Tumor-like and infiltrative lesions on the lower extremities in the patient reported on.

and neither attached to surrounding tissues nor matted together. No enlargement of the liver or spleen could be detected clinically. The temperature was normal, and there were no abnormal observations on the urine. Radiologic examination showed no evidence of disease in the chest; the Wassermann reaction of the blood was negative. The blood cell count was as follows: red blood cells 4,560,000, hemoglobin 74 per cent, color index 0.82, white blood cells 9,600, polymorphonuclear cells 77 per cent, lymphocytes 19.5 per cent, monocytes 3.5 per cent, no eosinophils and a plentiful supply of platelets. A diagnosis of mycosis fungoides was made, and treatment with sodium cacodylate was started. During the next few weeks the general condition remained unchanged, while new tumors appeared in different places. Later there were periods of remittent pyrexia, the temperature sometimes rising to 103 F., and no internal complications other than softening of the enlarged lymph nodes could be observed to account for this. It was influenced

for a time by treatment with "sulphamezathine" (2-sulfanilamido-4,6-dimethylpyrimidine) and later with penicillin. The enlarged nodes in the left groin became tender and the skin over them hot and ultimately ulcerated, the floor being covered with foul-smelling greenish slough. The skin, as a whole, had taken on a dark brown tinge, and numerous red-brown crusts were present on the forehead, preauricular region and chin. Death occurred on September 21.

Observations at Necropsy.—External: The body was wasted and the skin covered with lesions varying from small raised nodules to large semipedunculated masses 5 cm. in diameter. The masses were firm and buff-colored. Many of the larger ones showed surface ulceration and necrosis. Early ulcerated lesions were present on the face.

Lymph Nodes: The lymph nodes were greatly enlarged in the groins and in the axillas and consisted of masses of firm buff-colored tissue forming discrete nodules. There was a large ulcerated area in the left groin over the enlarged inguinal nodes. The lymph nodes along the aorta and the iliac vessels were greatly enlarged, forming discrete masses of firm buff-colored material.

Lungs: Congestion was present in the base of both lungs. The hilar and mediastinal nodes were not enlarged. There was no naked-eye evidence of infiltration.

Liver: The liver weighed 1,940 Gm.; it was slightly enlarged, but otherwise of normal appearance.

Spleen: The spleen was approximately twice normal size, 380 Gm.; the pulp was bright red and firm, with many small irregularly shaped deposits of buff-colored tissue.

Marrow: Marrow taken from the middle of the shaft of the left femur was semigelatinous and dark yellow.

Other Organs: There were no naked-eye abnormalities observed in other organs.

Histologic Studies.—In addition to the necropsy material, biopsy specimens of a small cutaneous nodule and an enlarged lymph node were taken.

Small Cutaneous Nodule (Biopsy): The surface epithelium at the margins was normal, but over the center of the nodule it was thin and papillae were absent. The whole thickness of the skin, right up to the lower surface of the epithelium, contained a dense cellular infiltration of diffuse type. These cells were moderate sized and polyhedral or oval, with slightly acidophilic cytoplasm. In places, the outlines of the cells were indistinct and the appearance was almost syncytial. The nuclei were large and oval or polygonal, with a well defined nuclear membrane and granular nucleoplasm containing one or more chromatin dots. No mirror-image cells were seen and only occasional multinucleated forms. Mitoses were moderately numerous. The infiltration was considered to be almost entirely of reticulum cell type (fig. 2 *A*).

Larger Cutaneous Nodule: The larger cutaneous nodule was characteristic of several necropsy specimens. Here there was a general cellular infiltration, as described in the smaller nodule, but more pleomorphic. In addition to the reticulum cells, there were plasma cells, monocytes, more multinucleated forms, a few eosinophils and varying numbers of polymorphonuclear leukocytes. The picture here was therefore more like that of a granulomatous disease than was the picture of the small biopsy nodule. Nuclear pyknosis, described more fully in the histologic study of the liver, was a feature of these more fully developed cutaneous lesions (fig. 2 *B*).

Lymph Node (Biopsy): The capsule of the lymph node was not thickened and nowhere invaded. Follicles were few in number and mostly small. The gross

anatomic structure of the lymphadenoid tissue was greatly disturbed by a diffuse cellular infiltration, which was generally dense and composed chiefly of cells of reticulum type similar to those seen in the skin. Mitoses were more numerous than

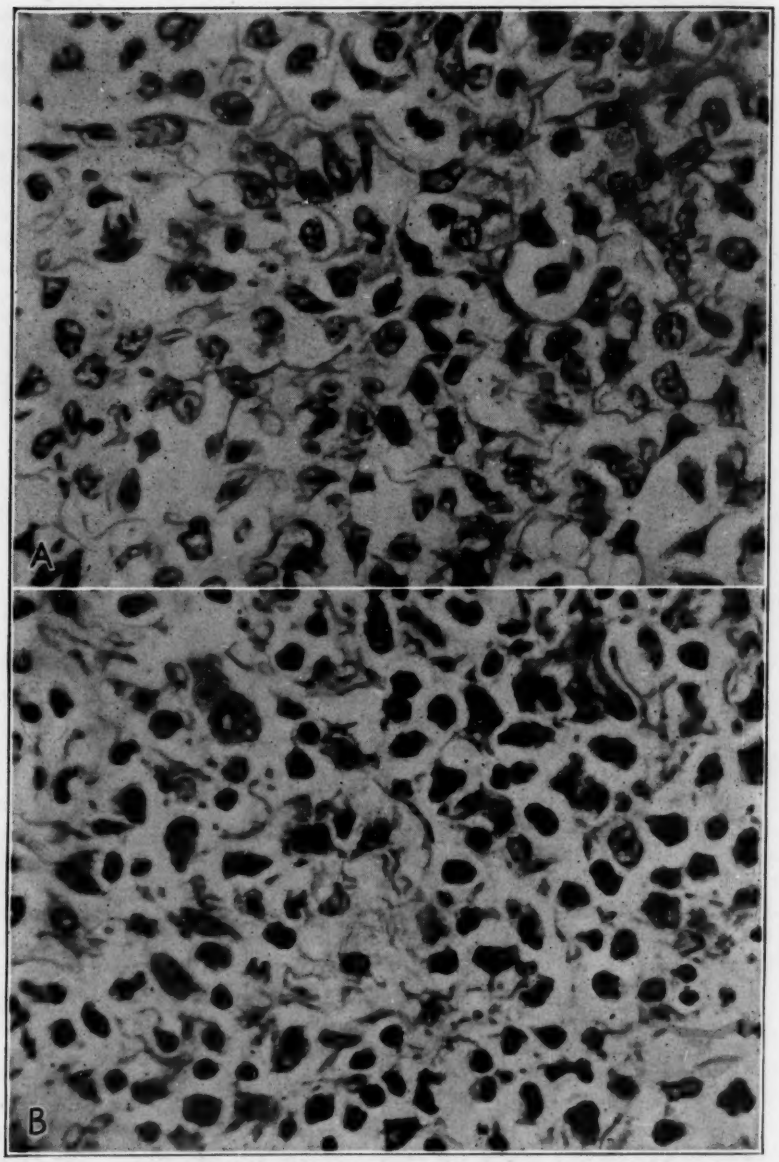

Fig. 2.—*A*, high power view of a small cutaneous nodule, showing diffuse infiltration of reticulum cells (hematoxylin and eosin, × 640). *B*, high power view of larger cutaneous nodule. Here the cellular infiltration is more pleomorphic and nuclear pyknosis is present (hematoxylin and eosin, × 640).

in the cutaneous nodule which was submitted for biopsy. Multinucleated cells were present in small numbers, and there were also a few plasma cells and eosinophils.

Typical Sternberg-Reed cells were not seen. No tendency toward increase of fibrous tissue was observed.

Liver: There were widespread cellular infiltrations, most pronounced in the periportal areas but also scattered indiscriminately in groups throughout the liver, with many isolated cells in the sinusoids. Most of these cells, while considered

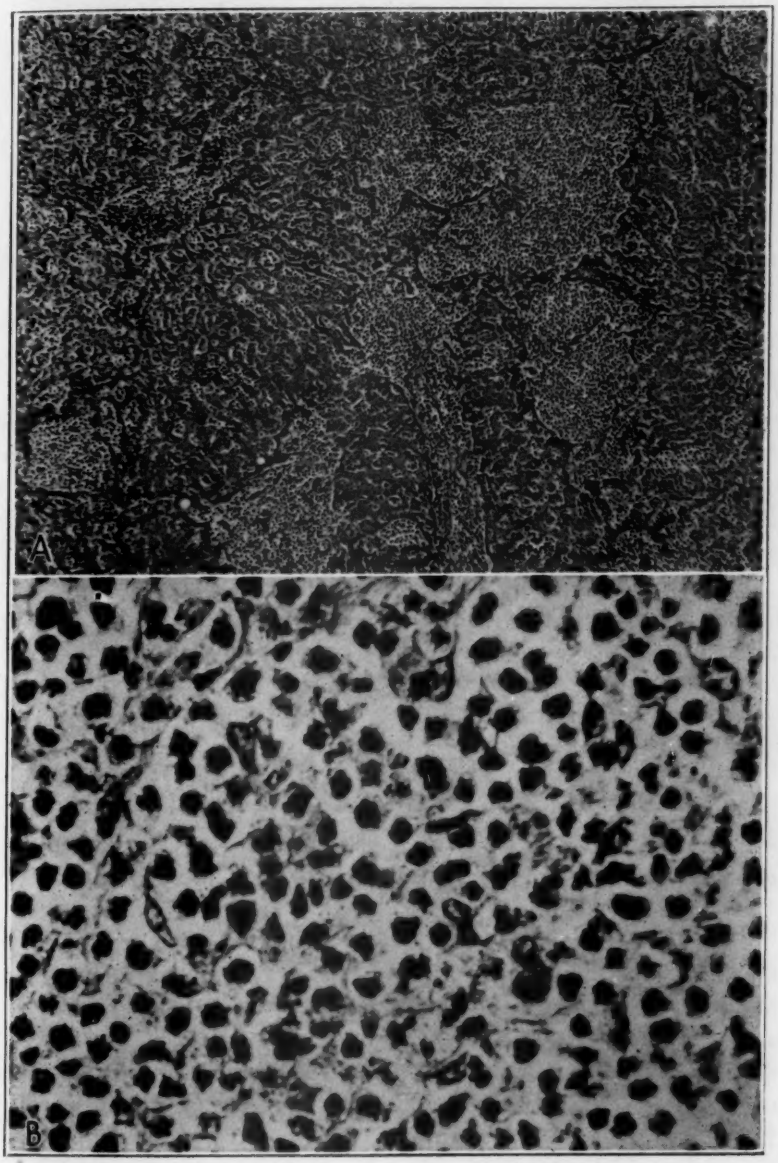

Fig. 3.—*A*, low power view of cellular infiltrations in the liver (hematoxylin and eosin, × 65). *B*, high power view of one of the infiltrations of the liver, showing the varied nuclear shapes and the pronounced pyknosis (hematoxylin and eosin, × 640).

to be of reticulum type, differed from those seen in the skin and lymph node by the fact that their nuclei had bizarre forms, often containing four, five or six large dots of nuclear chromatin connected by strands of similar material, and sometimes the nucleus had almost disintegrated into small darkly staining dots. The appearance was that of degenerative pyknosis. Occasional giant cells were seen, but no eosinophils or small lymphocytes. There was no tendency toward the deposition of fibrous tissue in connection with these infiltrations (fig. 3).

Spleen: The normal pattern was disturbed, and only occasional small lymph follicles were seen. The pulp was packed with cells similar to those seen in the liver and showed the same features of pronounced nuclear degeneration.

Kidney and Adrenals: No cellular infiltrations were seen in the kidney or adrenal glands.

COMMENT

The diagnosis of mycosis fungoides in this case is based on the clinical history and both naked-eye and microscopic appearance of the lesions.

The duration of the illness, from the time when the first symptoms were noticed to its fatal termination, was three years. The initial lesions, of eczematoid character, were succeeded by the development of infiltrated plaques, nodes, tumors and ulcers in the later stages. Some of the cutaneous tumors resembled raw tomatoes in color and shape and therefore appeared to be most characteristic of mycosis fungoides. In addition, various groups of superficial lymph nodes, the liver and the spleen were observed to be affected. There was complete absence of pathologic changes in the mediastinal nodes. The histologic picture of the nodules in the skin, lymph nodes and inner organs—a polymorphous infiltrate, chiefly reticulum cells with monocytes, plasma cells, eosinophils, lymphocytes and multinuclear cells, and the presence of numerous mitoses and nuclear changes, such as pyknosis and karyorrhexis—is no doubt consistent with the aforementioned diagnosis.

Not in all cases of mycosis fungoides, however, is the diagnosis obvious or easy. This must be borne in mind in order to understand one aspect of the disease, at least, which seems to have added so much to the confusion prevailing in regard to the relation of mycosis fungoides to other types of reticulosis.

Hodgkin's disease, above all, is a condition with which mycosis fungoides in its tumor stage is most likely to be confused, so much so that Senear and Caro (1937) [3] and, according to these authors, Ziegler [4] and also Milian, expressed the opinion that probably the two were identical morbid conditions. It cannot be denied that there are cases involving skin and inner organs in which, as Goldsmith [1] pointed out, either diagnosis would be justified. This, however, seems to prove the

3. Senear, F. E., and Caro, M. R.: Ulcerative Hodgkin's Disease of the Skin, Arch. Dermat. & Syph. **35**:114 (Jan.) 1937.

4. Ziegler, cited by Ormsby and Montgomery.[5]

limitations of the means of diagnosis rather than the identity of the two diseases.

Although our imperfect knowledge of the cause of and pathologic structure in both diseases does not allow for a final settlement of the problem, we propose to discuss it.

The following features are common to both mycosis fungoides and Hodgkin's disease:

1. The highest incidence is in middle age, though either disease may start at any time.

2. Male persons are more frequently affected than female.

3. Either disease runs a fatal course, the average duration, though varying within wide limits, being estimated by Ormsby and Montgomery (1943) [5] at five years in mycosis fungoides and three years in Hodgkin's disease.

4. Pathologically, both diseases are characterized by a proliferation of reticuloendothelial elements and, in a number of cases, by the presence of nodular and tumor-like lesions in the skin, lymph nodes and certain internal organs.

In considering the distinguishing features of the two diseases, it has to be noted that mycosis fungoides primarily affects the skin, the only reported exception to this being in Faber's case (1939),[6] in which internal organs were affected without cutaneous involvement. Enlargement of regional lymph nodes or general adenopathy follows in many cases, with or without specific histologic changes. Involvement of internal organs is generally accepted to be uncommon, although Berman (1940) expressed the opinion that it was the rule rather than the exception.[7] As to the frequency and order of involvement of the various organs, exactly the opposite holds true for Hodgkin's disease, in which the lymph nodes, subcutaneous, mediastinal and mesenteric, are primarily involved, and certain viscera, most frequently the liver and the spleen, are secondarily involved. Cutaneous manifestations are seen in 38 per cent of all cases (Goldman, 1940),[8] though a few exceptional cases of primary Hodgkin's disease of the skin have been recorded (Kren, cited by Ormsby and Montgomery, 1943, and Goeckerman and Montgomery,[9] 1931).

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5. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943.

6. Faber, V.: Zentralbl. f. allg. Path. u. path. Anat. **72**:152, 1939.

7. Berman, L.: Pathologic Nature of Mycosis Fungoides, Arch. Path. **29**:530 (April) 1940.

8. Goldman, L. B.: Hodgkin's Disease, J. A. M. A. **114**:1611 (April 27) 1940.

9. Goeckerman, W. H., and Montgomery, H.: Lymphoblastoma, Arch. Dermat. & Syph. **24**:383 (Sept.) 1931.

It is customary to divide the development of mycosis fungoides into three stages: premycotic, infiltrative and, finally, tumor formation. They may merge imperceptibly into one another, or an interval varying from a few weeks to many years may occur. The different stages may also overlap one another; our patient exhibited flat infiltrated plaques along with tumors and ulcers.

If cutaneous lesions are present in Hodgkin's disease, there is nothing in their character or order of appearance to suggest a subdivision into different stages. The cutaneous manifestations of Hodgkin's disease are usually classified under the head of (1) specific (nodules, tumors and ulcers) and (2) unspecific (generalized pruritus, with or without lichenification and pigmentation, papular, vesicular and urticarial eruptions, purpura, herpes zoster and exfoliative dermatitis or generalized erythroderma). No clue to the diagnosis can be expected from the histologic picture of the unspecific manifestations, since, as a rule, there is no characteristic infiltration. But even the specific cutaneous manifestations of Hodgkin's disease can hardly be differentiated on mere inspection from similar lesions of mycosis fungoides. A correct diagnosis can be arrived at only by careful consideration of the history, general clinical appearance and observations and, above all, by the histologic examination of the affected skin and the lymph nodes.

Little information can be obtained from the blood picture and the temperature chart. Neither of the two diseases has anything like a characteristic blood picture. A decided eosinophilia (over 10 per cent) in the blood is generally accepted to be more suggestive of mycosis fungoides, though eosinophilia is by no means a constant feature in this disease. The number of eosinophils in the blood of patients with mycosis fungoides varies within wide limits; in our patient there were none, whereas Brünauer (1925) [10] recorded as much as 70 per cent in a case.

Pyrexia of unknown origin is stated to be not uncommon in Hodgkin's disease. The fever is either irregular, remittent or intermittent over a period of months, with occasional minor rigors (Warner, 1944 [11]), or else of the Pel-Ebstein type. Likewise, pyrexia occurs in patients with mycosis fungoides. Twice in the last few weeks of his illness, our patient experienced fever of the remittent type, each period lasting seven days, with an interval of nine days between. Each time the rise of temperature coincided with acute inflammation, softening and disintegration of enlarged lymph nodes and could be brought under control with the administration of "sulfamezathine" or penicillin. The assumption is that the fever was caused through secondary invasion of the affected lymph nodes by pyogenic bacteria.

10. Brünauer, S. R.: Acta dermat.-venereol. **6**:131, 1925.

11. Warner, E. C.: Brit. J. Dermat. **56**:129, 1944.

From what has been said, it is evident that in a given case, in which there are suspected tumors and ulcers of the skin, with or without involvement of lymph nodes and internal organs, no diagnosis between mycosis fungoides and Hodgkin's disease can be made without consulting the microscopic picture of the lesions.

Proliferation of reticuloendothelial elements is present in the lesions of either disease. A decided degree of polymorphism, the presence of numerous mitoses, pyknosis, karyorrhexis and clumping of reticuloendothelial cells are regarded as the characteristic features of mycosis fungoides. It will be noted that the pronounced pyknotic nuclear changes seen in the cellular infiltrations in the liver and the spleen in our patient were similar to those described by Payling Wright in one of the cases discussed by Goldsmith.[1] It has also been pointed out by Freudenthal, cited by Robb-Smith, that the cell proliferation arises in the upper part of the cutis and spreads toward and into the epidermis. The principal distinguishing features of Hodgkin's disease are a hypertrophic sclerosis of the interstitial tissue, which is absent in sections of tissue from patients with mycosis fungoides, and the presence of Sternberg-Reed cells. It is, however, well to remember that multinuclear cells of varying shape are met with in sections of tissue from patients with mycosis fungoides, some of them occasionally resembling the Sternberg-Reed type to such a degree that it is not always easy to identify them. Laederich, Mamou and Beauchesne (1932) [12] claimed that accumulation of eosinophils in large groups is characteristic of Hodgkin's disease. From our own experience, we should not attach too much significance to this detail, as it is by no means uncommon to observe large amounts of eosinophils in specimens of tissue in mycosis fungoides.

Reference must finally be made to Gordon's elementary bodies and his test for Hodgkin's disease. No analogous observations have so far been reported with regard to mycosis fungoides. Provided that the specificity of Gordon's observations be taken for granted, this would mean another and conclusive link in the chain of evidence against the alleged identity of the two diseases.

Another problem encountered in reviewing the subject of mycosis fungoides, is the question as to its pathologic nature; in other words, is mycosis fungoides an inflammatory granuloma or a malignant neoplasm? Fraser (1925) [13] and others held that mycosis fungoides is a neoplasm, a reticulosarcoma, and in support of this view, attention has been drawn to the following observation:

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12. Laederich, L.; Mamou, H., and Beauchesne, H.: Bull. Soc. franç. de dermat. et syph. **39**:1357, 1932.

13. Fraser, J. F.: Mycosis Fungoides, Arch. Dermat. & Syph. **12**:814 (Dec.) 1925.

1. The clinical manifestations in a given case may be consistent with mycosis fungoides, whereas the histologic picture is that of reticulosarcoma.

2. Cases of apparent mycosis fungoides have been described as terminating in reticulosarcoma.

3. The lesions in the internal organs may be interpreted as metastases.

Robb-Smith [2] has dealt with this kind of argument in such a way that any attempt to comment on the matter would inevitably involve quotations of what he has written.

As to the first category of cases, it has already been pointed out that the histologic picture should be conclusive, and, consequently the disease in a case which from microscopic examination is adjudged to be reticulosarcoma is reticulosarcoma, no matter what its clinical appearance is like. The difficulty is largely one of determining when polymorphism is greater than could be expected in a reticulosarcoma, and this particular difficulty occurred in our case, in which the first small nodule examined presented an almost pure reticulum cell infiltration, while larger and more fully developed lesions in the skin showed a more mixed cell pattern.

With regard to cases of apparent mycosis fungoides terminating in reticulosarcoma, Robb-Smith [2] pointed out that it may be difficult "to distinguish between a progressive hyperplastic condition and a blastoma. . . . though it is uncommon, many reticuloses do undergo sarcomatous change, and there is no reason why mycosis fungoides should not occasionally undergo such a change. . . ." In other words, the fact that an odd case of genuine mycosis fungoides may turn into reticulosarcoma does in no way prove the primary neoplastic nature of mycosis fungoides. It is, however, highly probable that those cases in which the disease has been referred to as mycosis d'emblée may belong in a different category, as, according to Ormsby and Montgomery,[5] the disease in many of them has proved to be reticulosarcoma from the beginning.

With reference to the involvement of internal organs in mycosis fungoides, Robb-Smith said: "If one accepts the concept of multicentric autochthonous proliferation of systematization in the reticuloses, there is no need to regard the presence of mycotic proliferations in lymph nodes, liver or spleen as evidence of embolizing metastases." In fact, the way in which these "secondary" manifestations are confined to certain organs, noticeable through their relation to the reticuloendothelial system, as well as the absence of any destructive expansion of the lesions in both the skin and the viscera, is far more indicative of an inflammatory granuloma with special affinity to the reticuloendothelial system than of a malignant neoplasm.

Cell polymorphism and the presence of numerous mitoses in the morbid tissue, along with degenerative nuclear changes and the formation of giant or pseudo giant cells, could perhaps be interpreted as signs of malignant growth, though it is hard to see what kind of growth it could be that is made up of such a variety of cell types. Moreover, it is remarkable that even in as advanced a case as that reported herein no sign of destructive expansion of the infiltrate could be detected in the sections of the cutaneous or visceral lesions. True, the cellular infiltration, where it is present, is extremely dense. In the skin it occupies the whole cutis and penetrates into the subcutis; the connective tissue is accordingly rarefied and to a great extent replaced by the infiltrate. The structure of the sweat glands, however, where they are observed to be closely surrounded by and embedded in the cellular infiltrate, is intact. Analogous conditions prevail, *mutatis mutandis,* in the lesions of the lymph nodes, liver and spleen. The balance of histologic evidence is therefore unmistakably in favor of inflammatory granulation tissue and against blastoma.

Finally, the concept of mycosis fungoides as an infectious granuloma seems to win support on the basis of results of inoculation of animals. Brünauer (1925) [10] inoculated guinea pigs with mycotic tissue taken from various affected organs of a patient. Nine weeks after subcutaneous inoculation with material of a nodule from the human spleen, in 1 animal out of 9, lesions had developed on the inner aspect of the sternum as well as in the liver and spleen. In histologic structure these lesions closely resembled each other and the original nodule. More recently Stratton (1943) [14] reported positive results obtained by inoculation of white mice with an emulsion of cutaneous mycosis fungoides nodules.

SUMMARY

A case of mycosis fungoides affecting the skin and internal organs is described. The histologic structure of biopsy and autopsy material is given.

The pathologic structure and differential diagnosis of this disease are discussed; the features distinguishing it from Hodgkin's disease are stressed, and the reasons are adduced for considering mycosis fungoides to be an infective granuloma rather than a blastoma.

14. Stratton, E. K.: Mycosis Fungoides, Arch. Dermat. & Syph. **48**:179 (Aug.) 1943.

HEREDITARY PREDISPOSITION IN VASCULAR DISTURBANCES OF THE LEG

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HELLER,[1] in considering the various types of indolent ulcers of the leg, grouped them under three headings: (1) true varicose ulcers, (2) ulcers with a varicose background plus another factor, such as cardiac disease, occlusive arterial or occlusive inflammatory venous disease, or ulcers with a background of functional venous disturbance due to impairment of muscular activity or to obesity and (3) ulcers due to any of these factors without varicose veins. All these conditions have as a common factor ischemia arising from peripheral arterial or venous disturbance and leading to cutaneous dystrophy. Since

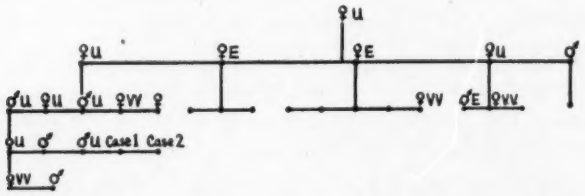

Chart showing familial occurrence of vascular disturbances of the leg. The letter *U* indicates ulcer, *E* eczema of the leg and *VV* varicose veins.

this dystrophy is the sequel of impaired blood supply, one would naturally anticipate its occurrence in diseases not only of the blood vessels but of the blood itself. This association has, in fact, been observed. Witts,[2] in describing a chronic ulcer of the leg in a case of purpura hemorrhagica, pointed out that, whereas ulcers are associated with sickle cell anemia, acholuric jaundice, Gaucher's disease and splenic anemia, they are apparently not observed with pernicious anemia or chlorosis.

Weber, Rast and Lutterotti[3] recorded a case of an Englishman, aged 25, who had a large indolent ulcer of one leg, surrounded by much pigmentation, and on the other leg similar pigmentation and scars. His father had suffered from chronic ulcers of the leg for thirty years, of

From the Skin Department, Radcliffe Infirmary.

1. Heller, R. E.: Surg., Gynec. & Obst. **76**:77, 1943.
2. Witts, L. J.: Brit. M. J. **2**:309, 1942.
3. Weber, F. P.; Rast, H., and Lutterotti, O.: Brit. M. J. **2**:279, 1930.

a severity so disabling that he had to have one leg amputated. Gangrene supervened in the stump, necessitating higher amputation. The amputated stump was microscopically examined, and some periarterial matting was seen. In a private communication Parkes Weber described another family with a striking history of chronic ulcer of the leg in male as well as female members.

The following case histories are further evidence of a hereditary factor predisposing to local vascular disturbance leading to ulceration.

REPORT OF CASES

CASE 1.—Miss S., a slim woman of 45, presented a small ulcer which had developed six years prior to examination on the medial side of the left leg, just above the malleolus. This remained small for about five years and then suddenly spread and became painful and malodorous, with some surrounding dermatitis. Before the appearance of the ulcer the skin of the leg looked normal, the veins were not varicose and there had been no trauma. She was treated with penicillin cream and a skin graft. Cheered by a good result, she produced her sister, Mrs. G.

CASE 2.—Mrs. G., aged 40, first noticed a brown spot on the inner side of her left leg, above the malleolus, eleven years prior to examination. This later broke down and ulcerated. It remained much the same, with improvements and relapses, until two years ago, when it spread to involve the lower third of the leg on the inner side. She received the same treatment as her sister, with equally good results.

The family history of these 2 patients goes back to a great-grandmother who had a varicose ulcer. Of her 5 children, 2 had varicose eczema and 2 ulcers of the leg. The grandmother of the patients had an ulcer and of her 5 children, 3 had ulcers and 1 varicose veins. The patient's father had an ulcer and of his 5 children, 4 had ulcers. In the next generation, it was only possible to get 2 case histories, from a nephew and a niece of the patients. The niece, aged 24, had exceptionally bad varicose veins. The family history may be even more striking than appears, since the offspring of the 3 affected grandaunts were not well known to the patients and may have had lesions, of which they had not heard.

To these cases may be added 2 of a somewhat different nature.

CASE 3.—Mrs. S., aged 70, showed on the front of the left ankle an ill defined patch, where the skin felt colder and thicker than the normal skin. It was bluish, with telangiectases and a *pélure d'oignon* surface. About fifteen years before the present examination a similar patch appeared on the other leg, but it spread and altered. There was from the middle part of the calf to the ankle a gaiter of pseudoscleroderma. The subcutaneous tissue had become atrophic, binding down the skin to the underlying tissues. Over the atrophic area the epidermis was scaly and rather shiny. The disease was slowly spreading up the leg. In the winter, the part of the leg above the affected area became greatly swollen and edematous, "as if there were an iron band round the lower part." Mrs. S. was otherwise a healthy woman, with no cardiac disturbance. The Wassermann reaction was negative.

CASE 4.—Miss S., aged 39, daughter of the patient described in case 3, presented a patch, which had recently developed above the right ankle, of cyanotic finely pleated skin with telangiectases. It exactly resembled the patch on her mother's left leg. She was otherwise healthy. The Wassermann reaction was negative.

These cases of relatively mild cutaneous dystrophy are difficult to place. They approach the category of acrodermatitis chronica atrophicans. But Oppenheim, cited by Sutton,[4] limited this name to the disease characterized by (*a*) doughy infiltration at the onset, (*b*) the presence of ulnar bands, (*c*) localization on the extensor surfaces, especially of the knee, elbow and fingers, and (*d*) absence of involvement of the entire body. Oppenheim expressed the belief that this disease is due to an external agent acting on predisposed skin, whereas the macular and diffuse forms of dermatitis atrophicans were ascribed by him to an internal causative agent, but again acting on predisposed skin. In both groups predisposition is, therefore, an important factor.

The disease known as atrophoderma neuriticum is invariably secondary to neuritis. De Takats [5] stated the belief that venous thrombosis and periphlebitis, as well as trauma, can activate a nutritional reflex and give rise to local vasomotor and trophic phenomena. He further claimed that these reflexes occur more easily in mentally unstable and defective persons. Predisposition, therefore, is not necessarily limited to the cutaneous tissues.

The disease in case 3 had a certain resemblance to the atrophoderma albidum of Kaposi, cited by Pusey,[6] with its stocking-like distribution. But this disease appears in early childhood and remains stationary. There is still much doubt as to the exact interrelationship of scleroderma, scleropoikiloderma, acrodermatitis atrophicans, macular diffuse dermatitis atrophicans and the numerous unclassified *formes frustes* that one encounters. It is therefore premature to do more than speculate on the presence of a local predisposition of the tissues to atrophic changes or a local vascular instability acting alone or affecting the nerves of the skin. Hereditary predisposition has already been suggested for some of these diseases. The 2 cases herein briefly recorded give further evidence to the same effect.

SUMMARY

A striking family history is recorded in 2 cases of varicose ulcers in sisters.

Two cases of pseudoscleroderma of the leg are described in a mother and daughter.

The hereditary factor in these diseases deserves further inquiry.

45 Banbury Road.

4. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939.

5. de Takats, G.: Reflex Dystrophy of Extremities, Arch. Surg. **34**:939 (May) 1937.

6. Pusey, W. A.: Principles and Practice of Dermatology Designed for Students and Practitioners, New York, D. Appleton and Company, 1924.

SARCOIDOSIS

Report of an Atypical Case with Erythrodermic Lesions, Subcutaneous Nodes and Asteroid Inclusion Bodies in Giant Cells

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AND
DAVID G. FREIMAN, M.D.
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A CASE of sarcoidosis with several unusual features recently came under observation. The patient presented erythrodermic lesions, a rare manifestation of sarcoidosis, together with subcutaneous nodes consistent with those described as Darier-Roussy's sarcoid. In addition, histologic examination of the nodes revealed asteroid inclusion bodies in giant cells.

REPORT OF A CASE [1]

A 45 year old caretaker first noticed, in the fall of 1942, red slightly scaling patches on the inner aspects of the thighs, in the groins and on the lower part of the abdomen. A few months later similar patches appeared in the right axilla and the right popliteal space. The lesions, which were asymptomatic, slowly increased in size. Early in 1944 the patient noticed additional red patches in the left axilla, on both ankles and on the dorsal aspects of the feet. In March 1944 nontender firm subcutaneous nodes began to appear on the thighs, in the left groin and, a short time later, on the face, chest, abdomen and right buttock. The patient was first seen at the Massachusetts General Hospital on September 18. He appeared healthy and had no complaints except for slight soreness in the left groin.

Physical examination revealed diffuse erythema involving the lower part of the abdomen (fig. 1*A*), the groins and the upper third of the anterior and medial aspects of the thighs. A large patch of erythema was present in each axilla, extending to the breasts and the lateral walls of the thorax (fig. 1*B*). There was a large erythematous patch in the right popliteal space and smaller patches on both ankles and on the dorsa of the feet. The areas of erythema were for the most part fairly well demarcated. They were covered with fine silvery easily detachable scales, and the natural furrows of the skin appeared slightly exaggerated. On palpation no infiltration could be felt. In the areas of erythroderma the hair was sparse. The axillas were almost entirely devoid of hair. Besides the large patches of erythema, there were on the abdomen, the thighs, legs and buttocks scattered brownish red noninfiltrated macules with superficial scaling. Twenty-three subcutaneous nodes were palpable. The smallest node measured 1 cm. in diameter, the largest, located in the left groin (fig. 2*A*), measured 12.5 by 5.5 cm. Eight of

From the Departments of Dermatology and Pathology, Massachusetts General Hospital.

1. Lever, W. F.: Giant Cell Reticulosis, Arch. Dermat. & Syph. **53**:180 (Feb.) 1946.

the nodes were larger than 3 cm. in diameter. The distribution of the nodes was as follows: one was located beneath the mucous membrane of the lower lip, one on the right side of the chin, two below the right nipple, one on the right side of the abdomen (fig. 1*A*), one in the left inguinal region (fig. 2*A*), five on the anterior, three on the medial, four on the lateral (fig. 2*B*) and one on the posterior aspect of the right thigh, one on the anterior and two on the lateral aspect of the left thigh and one on the upper inner quadrant of the right buttock. The smaller nodes lay free in the subcutaneous fat; the larger ones were attached to the skin, which was purple and thinned out above them. The large node in the left inguinal region showed central ulceration, with discharge of small quantities of a seropurulent fluid (fig. 2*A*). Eighteen nodes were located within areas of erythema and five nodes outside of such areas. On palpation, some nodes felt hard while

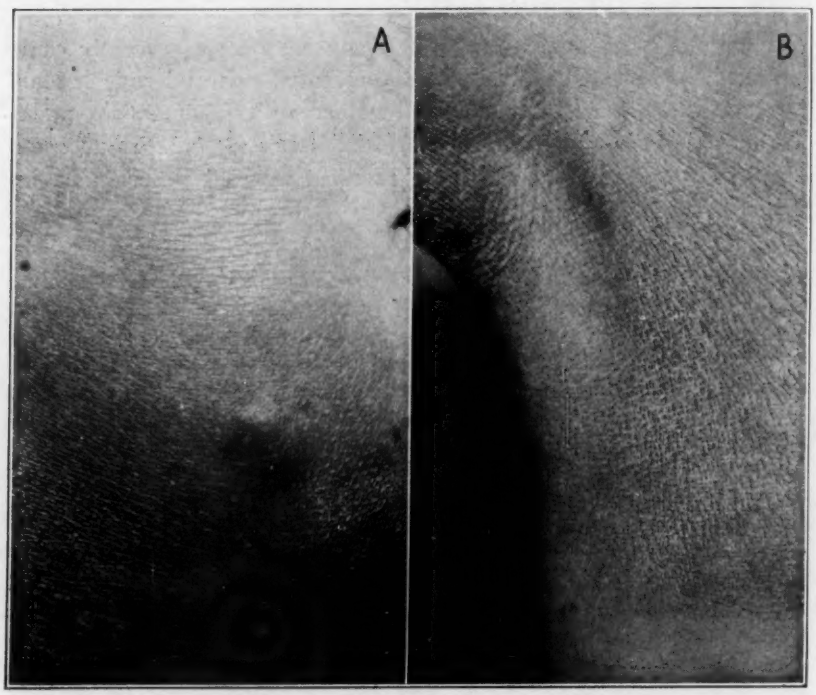

Fig. 1.—Diffuse erythroderma. *A*, abdomen and right groin. There is exaggeration of the natural furrows of the skin. Under the skin of the abdomen a node is visible, which on palpation felt as large as a walnut. *B*, right breast and right axilla. The border of the erythroderma is fairly distinct.

others felt moderately soft. All were nontender, fairly sharply demarcated and of irregular contour. Those located on the anterior and lateral aspects of the right thigh were in part confluent.

The physical examination revealed no other abnormalities.

In order to determine the effect of roentgen rays on the lesions, 300 r were administered to a subcutaneous node located on the left side of the chest. No change was noted either clinically or histologically.

Laboratory Studies.—Three blood cell counts revealed the percentage of monocytes to be 10, 12 and 12, respectively. Urinalysis revealed nothing abnormal. The

values for the serum calcium, phosphorus, potassium, nonprotein nitrogen, albumin and globulin were normal. Similarly, the values for lecithin, cholesterol, cholesterol esters, total fats and neutral fats in the whole blood, the plasma and the red cells were normal. The value for the blood sugar and the reactions in a sugar tolerance test and an insulin tolerance test were within normal limits. Roentgenograms of the chest and of the bones of the hands and feet as well as roentgenologic studies of the gastrointestinal tract revealed no pathologic changes. Reactions to intracutaneous injections of 0.1 cc. of old tuberculin in concentrations of 1 to 100,000, 1 to 10,000 and 1 to 1,000 were negative. A concentration of 1 to 100 produced an area of erythema measuring 2.5 cm. in diameter, with central induration. Inoculation of material from two nodes into guinea pigs produced no lesions.

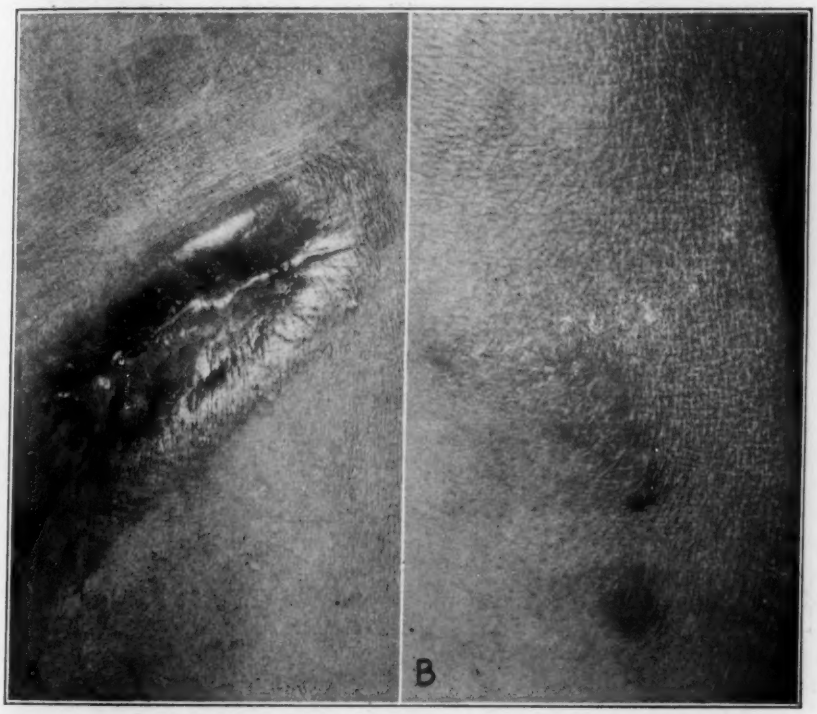

Fig. 2.—Subcutaneous nodes. *A*, a large subcutaneous node in the left groin, with central ulceration. *B*, four subcutaneous nodes on the lateral aspect of the right thigh. Two of the nodes have become confluent.

Reactions in a serologic test for syphilis (Hinton) and the Frei test for lymphogranuloma venereum were negative.

Histologic Examination.—The first two specimens for biopsy were taken from nodes located on the lateral aspect of the right thigh and on the left side of the chest, respectively. These two lesions were located outside areas of erythroderma and were firm. In both specimens the epidermis was thinned. The corium and subcutaneous fat showed extensive fibrosis. In many areas the connective tissue had a whorl-like arrangement around islands composed of epithelioid and giant cells or, occasionally, only of one or several giant cells (fig. 3*A*). The number of epithelioid cells was greatest at the lower borders of the nodes. The nodes were

fairly sharply demarcated toward the subcutaneous fat, with only slight infiltration of epithelioid cells and lymphocytes between the fat cells (fig. 3*B*). Many of the giant cells contained asteroid inclusion bodies.

A section taken from an erythrodermic lesion revealed an epidermis of normal thickness, with some flattening of the rete cones. A band of dense cellular infiltration occupied the upper part of the corium and consisted largely of monocytes together with moderate numbers of lymphocytes, rare epithelioid cells and a few eosinophils (fig. 4). Numerous blood capillaries were present. In most places a thin layer of connective tissue separated the band of infiltration from the epidermis, but here and there the epidermis was invaded. Small cellular foci of similar composition were present around the blood vessels of the deeper part of

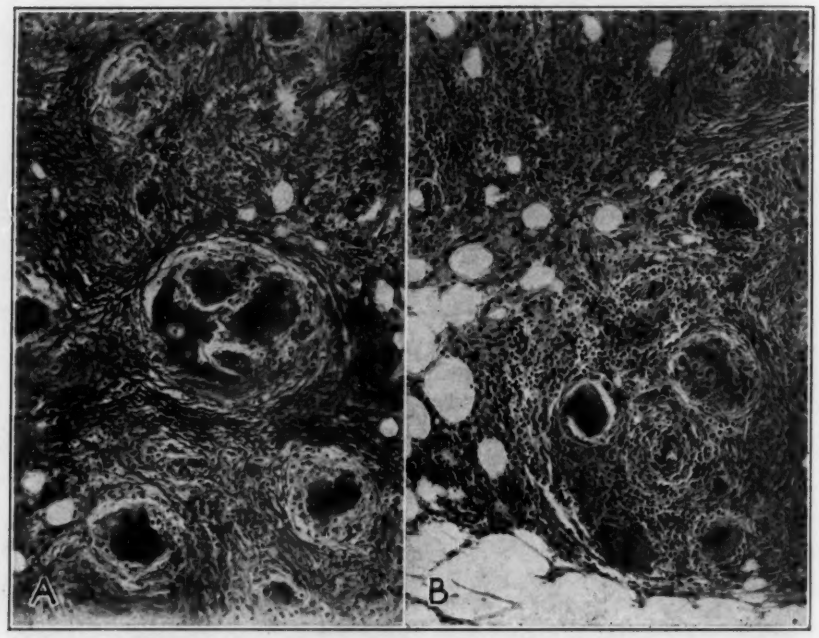

Fig. 3.—Sections from a subcutaneous node in the late healing phase (phloxine-methylene blue stain). *A*, center of the node. There is whorl-like arrangement of the connective tissue around islands composed of giant cells. *B*, border between the node and the subcutaneous fat. The border is fairly sharp, with only slight infiltration of epithelioid cells and lymphocytes between the fat cells.

the corium, around some of the sweat glands and in the subcutaneous fat (fig. 5). Not a single giant cell could be seen.

A section from a fairly soft node on the right side of the abdomen, located within an area of erythroderma, showed the following histologic picture (fig. 6). The band of infiltration in the upper part of the corium was composed of numerous epithelioid cells intermingled with lymphocytes and monocytes. In a few areas within the band of infiltration, especially toward its lower border, there were well defined granulomatous foci which tended to fuse with the underlying node. Occasional giant cells were present in these foci. Beneath this, occupying the lower part of the corium and largely replacing the subcutaneous fat, the node consisted of confluent granulomas made up of epithelioid cells, scattered large

giant cells and extensive fibrosis, a picture closely resembling that seen in the first two biopsies. The lateral and deepest portions of the node showed less fibrosis, but as in the uppermost portions, epithelioid and a few giant cells intermingled with monocytes and lymphocytes. Here and there in the subcutaneous fat close to the node there were small foci of cellular infiltration, composed of lymphocytes and monocytes and containing only a few epithelioid and giant cells.

There was no evidence of caseation in any of the sections, nor did appropriate stains reveal any acid-fast bacilli. Silver impregnation (Foot) (fig. 7) revealed a dense reticulum network throughout the subcutaneous nodes. In most areas the

Fig. 4.—Erythrodermic lesion (phloxine-methylene blue stain). A dense band of infiltrate composed of monocytes and lymphocytes occupies the upper part of the corium. The lower part of the corium is free from any infiltration. The infiltrate has invaded the epidermis.

reticulum fibers tended to surround almost every epithelioid cell, but in some the fibers were concentrated at the periphery of the granulomatous foci, leaving the central portions relatively free. A number of such areas contained one or several large giant cells, but this was not invariably the case. There was extensive collagen condensation around and extending into many of the foci, apparently along the reticulum, and mature connective tissue fibers were readily demonstrated by aniline blue and phosphotungstic acid hematoxylin stains.

The giant cells seen in the subcutaneous nodes varied greatly in size and shape. Some presented as many as thirty nuclei in a cross section. In a few these were located at the periphery, as in Langhans giant cells, but in most they were irregularly distributed or massed in the center. Some giant cells had a foamy cytoplasm (fig. 8*A*) and thus resembled Touton giant cells; others contained large irregular vacuoles, occasionally in such number as to break up the continuity of the cell (fig. 8*B*). Sudan III stains revealed lipid material in the small and a few of the large vacuoles, as well as in some of the epithelioid cells. Most of the large vacuoles, however, including all those in which asteroid bodies were present, contained none. On polariscopic examination the lipid material proved to be doubly refractile.

Asteroid bodies were present in about 3 per cent of the giant cells. They occurred with greater frequency in the giant cells located in areas of fibrosis than

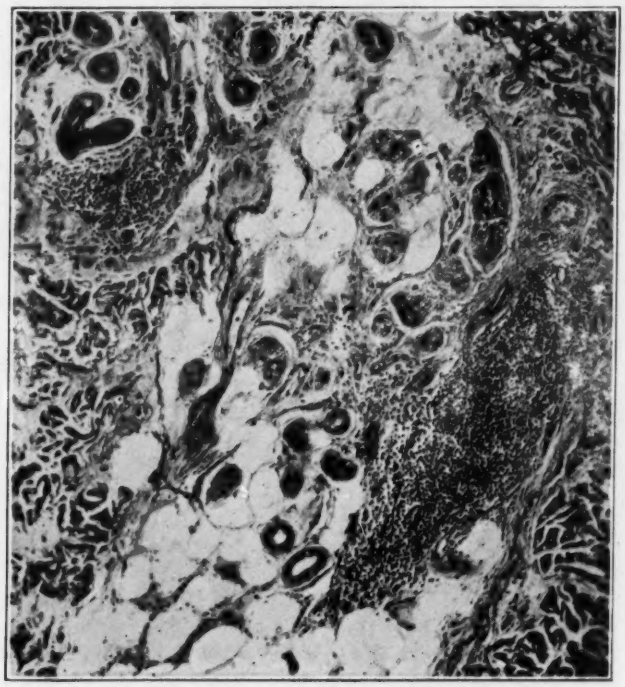

Fig. 5.—Erythrodermic lesion (phloxine-methylene blue stain). There are foci of cellular infiltration, largely composed of monocytes and lymphocytes, in the region of the sweat glands.

in those located in cellular areas. There were usually only one, but occasionally two or even three or four asteroid bodies in a giant cell, always located within a vacuole. Some were rather indistinct, showing no body but only faint radiating thin spikes (fig. 6). Others had a distinct round body from which slender tapering spikes radiated (fig. 8*A*). Since they could be seen in unstained sections, they were definitely not artefacts of staining. Of the various stains employed for the study of the asteroid bodies, phosphotungstic acid hematoxylin stained them best, because, in contrast to other stains, the body was differentiated from the spikes: the body stained brownish red and the spikes blue; occasionally a blue-staining central body

was present (fig. 9). These central bodies could not be visualized with any of the other stains employed. Elastic tissue stains revealed no elastic fibers within the asteroid bodies or in any of the giant cells. Sections of sternal bone marrow revealed no abnormalities.

Follow-Up.—The patient was seen at intervals. At the time of the last examination, in February 1946, there were no new subcutaneous nodes and those present had not changed. The erythematous lesions, however, had increased somewhat in extent. The patient felt well.

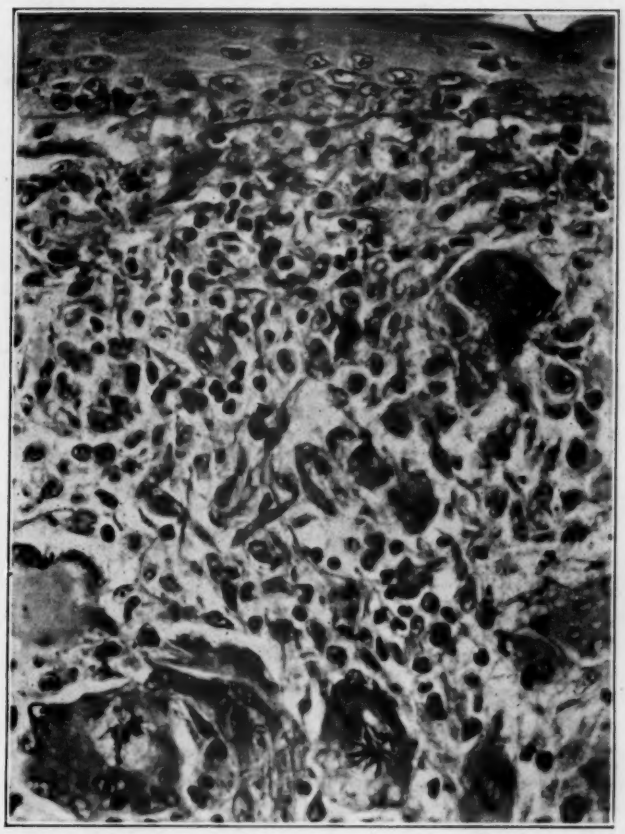

Fig. 6.—Section from a subcutaneous node in the early phase (Verhoeff elastic tissue stain counterstained with Van Gieson stain). The infiltrate is composed largely of epithelioid cells, with only a few scattered lymphocytes and monocytes. There is no evidence of fibrosis. Several giant cells are present; two of them contain asteroid bodies.

COMMENT

Clinical Aspects.—Prior to the performance of biopsies it was assumed that the case was one of lymphoblastoma, probably mycosis fungoides, because of the presence of subcutaneous nodes and of extensive areas of erythroderma. The only feature in discord with this diagnosis was the absence of itching in the erythrodermic areas. On the basis of

the first two biopsies, a diagnosis of giant cell reticulosis (Stengel-Wolbach sclerosis) was made. After performance of additional biopsies, however, sarcoidosis was considered the likeliest diagnosis. The cutaneous lesions were regarded as the erythrodermic form of Boeck's sarcoid and the subcutaneous lesions as subcutaneous sarcoid (Darier-Roussy's sarcoid).

Erythrodermic Form of Sarcoidosis: So far, 8 cases of sarcoidosis with erythrodermic lesions have been described, all of them in the European literature.[2] In all cases there were, in addition to the erythro-

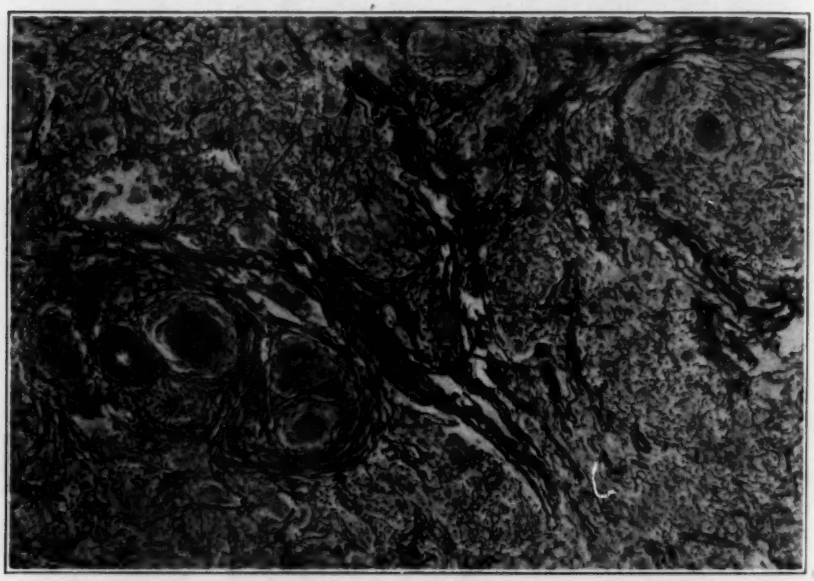

Fig. 7.—Section from a fibrotic node (reticulum silver stain [Foot]). A dense network of reticulum fibers is present.

2. Schaumann, J.: Sur une forme erythrodermique du lymphogranulome bénin, Ann. de dermat. et syph. **1**:561, 1920. Rischin, M.: Universelles benignes Miliarlupoid Boeck mit Beteiligung innerer Organe, Arch. f. Dermat. u. Syph. **139**:30, 1922. Schaumann, J.: Observations cliniques, bactériologiques et sérologiques pour servir à l'étiologie de la lympho-granulomatose bénigne, Bull. Soc. franç. de dermat. et syph. **41**:1296, 1934. Maschkilleisson, L. N., and Jakubson, A. K.: Zur Klinik des Boeckschen Sarkoids: Ein Fall von diffus-infiltrierender, teilweise erythrodermatischer Form, Dermat. Wchnschr. **98**:718, 1934. Hellerström, S.: Forme érythrodermique de lymphogranulome bénin, vérifiée par l'histologie, Zentralbl. f. Haut- u. Geschlechtskr. **51**:3, 1935. Pautrier, L. M.: Les lésions érythrodermiques pures de la maladie de Besnier-Boeck-Schaumann, Ann. de dermat. et syph. **7**:433, 1936. Nordin, G.: Morbus Schaumann (Lymphogranulomatosis benigna) mit Erythrodermie-Plaques und Iridozyklitis als vorherrschende klinische Symptome, Acta dermat.-venereol. **18**:245, 1937. Pautrier, L. M.: Le syndrome de Heerfordt des ophthalmologistes n'est qu'une forme particulière de la maladie de Besnier-Boeck-Schaumann, Ann. de dermat. et syph. **9**:161, 1938.

dermic lesions, lesions of sarcoidosis in organs other than the skin, and in 6 cases infiltrated, nodular or plaquelike lesions of the skin were also present. In none, however, were there subcutaneous lesions.

The erythrodermic lesions of sarcoidosis vary greatly in size. They have a fairly sharply demarcated border, which in the larger lesions tends to be irregular and serpiginous. In some cases, islands of normal skin are

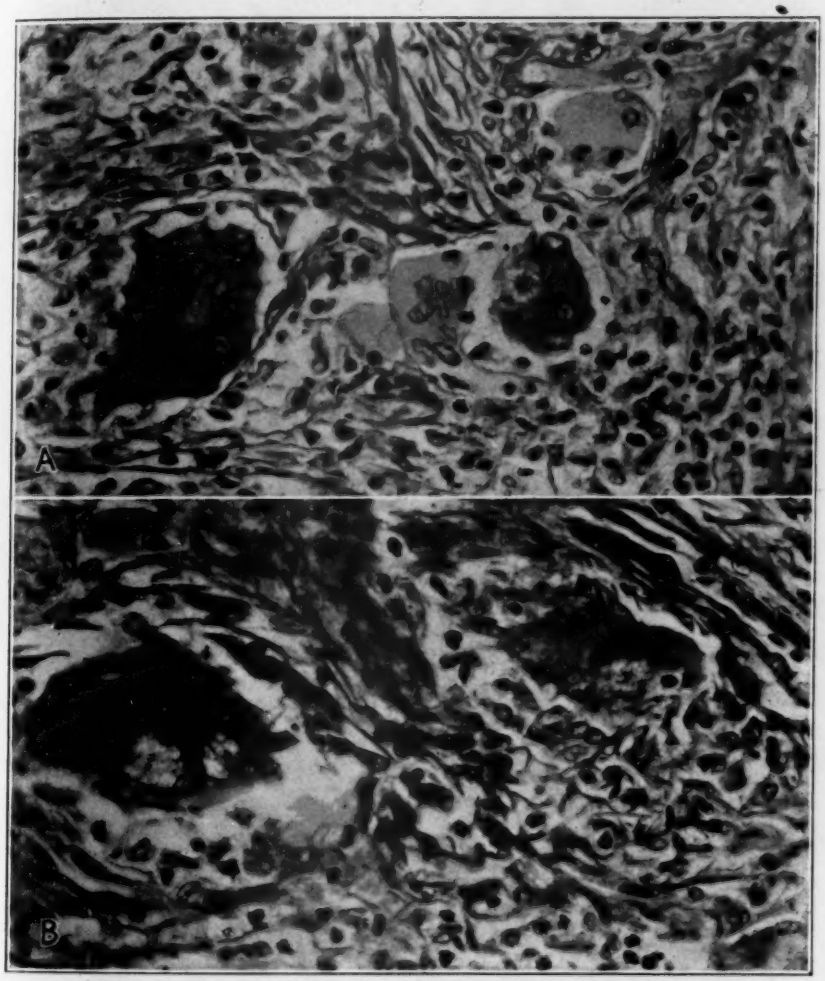

Fig. 8.—Giant cells (phloxine-methylene blue stain). *A*, five giant cells. Three of them have a foamy cytoplasm. One of the other two giant cells contains an asteroid body. *B*, two giant cells with large vacuoles.

present within the areas of erythroderma. The lesions show slight or no infiltration. The cutaneous markings are apt to be exaggerated. In some cases, fine silvery easily detachable scales cover the surface. Itching is regularly absent. Several authors have stressed the close resemblance of the erythrodermic lesions of sarcoidosis to those of mycosis

fungoides and the absence of itching in sarcoidosis as the most important differential diagnostic signs. Histologically the cellular infiltrate was in the majority of the reported cases limited to the immediate surroundings of the blood vessels, follicles and sweat glands, but occasionally was diffuse throughout the upper part of the corium. While the infiltrate was described as having the appearance of sarcoidosis in the cases previously reported, in our case only the erythrodermic areas in the vicinity of the nodes showed epithelioid cell granulomas; elsewhere the infiltrate was composed almost entirely of monocytes and lymphocytes.

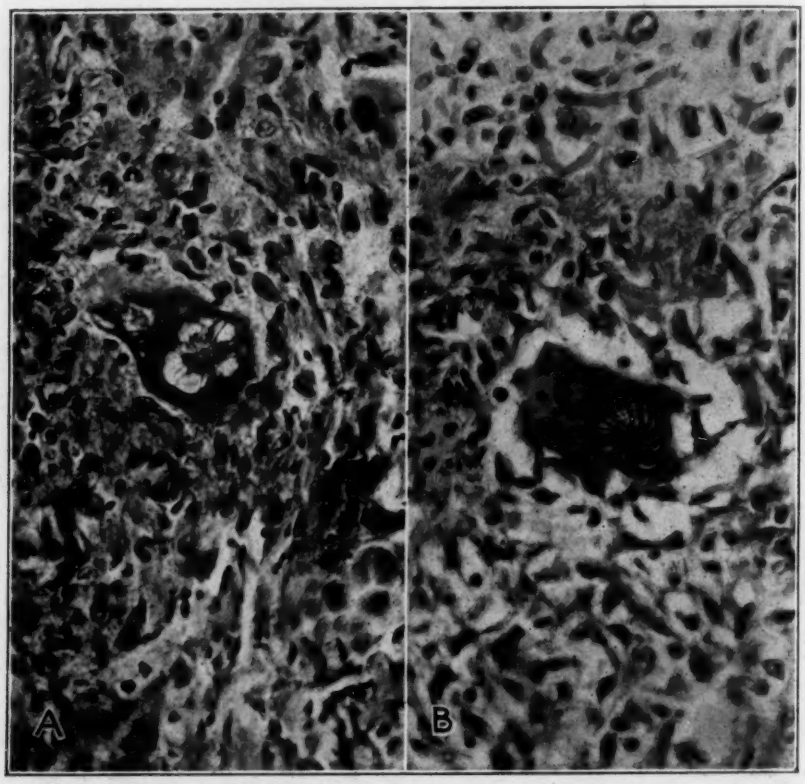

Fig. 9.—Asteroid bodies (phosphotungstic acid stain). Each of the two asteroid bodies is located within a vacuole and shows a central body.

Subcutaneous (Darier-Roussy's) Sarcoid: The term subcutaneous (Darier-Roussy's) sarcoid has been surrounded by confusion almost from the time it was introduced by Darier and Roussy in 1904.[3]

3. (*a*) Darier, J., and Roussy, G.: Un cas de tumeurs benignes multiples (sarcoïdes sous-cutanées ou tuberculides nodulaires hypodermiques), Ann. de dermat. et syph. **5**:144, 1904. (*b*) Darier, J.: Deux nouveaux cas de sarcoïdes multiples sous-cutanées, ibid. **5**:347, 1904. (*c*) Darier, J., and Roussy, G.: Des sarcoïdes sous-cutanées, Arch. de méd. expér. et d'anat. path. **18**:1, 1906.

Originally these authors regarded the lesions as identical with those of cutaneous ("Boeck's") sarcoid, but in 1918 Darier [4] alined Darier-Roussy's sarcoid with erythema induratum as "varieties of the same species."

A review of the recent literature on Darier-Roussy's sarcoid reveals that most American and English authors [5] tend to identify Darier-Roussy sarcoid with Boeck's sarcoid. German authors [6] generally agree that Darier-Roussy's sarcoid is erythema induratum. Schaumann [7] held a similar view. Beintema [8] expressed the belief that some cases of Darier-Roussy's sarcoid represent Boeck's sarcoid and others erythema induratum. Pautrier [9] and Maloney and Combes [10] regarded Darier-Roussy's sarcoid as a syndrome, frequently of tuberculous but occasionally of other genesis. Authors like Pinner [11] and Greschebin,[12] who expressed the opinion that sarcoid is a noncaseating type of tubercu-

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4. Darier, J.: Précis de dermatologie, ed. 2, Paris, Masson & Cie, 1918, pp. 292 and 637.

5. (*a*) Finnerud, C. W.: A Clinical, Histologic and Bacteriologic Study of a Case of Multiple Benign Sarcoid of Boeck-Darier-Roussy, Arch. Dermat. & Syph. **4**:342 (Sept) 1921. (*b*) Barber, H. W.: A Case of Benign Lymphogranuloma (Schaumann), Brit. J. Dermat. **39**:366, 1927. (*c*) Gray, A. M. H., in discussion on Barber.[5b] (*d*) Goeckerman, W. H.: Sarcoids and Related Lesions: Report of Seventeen Cases; Review of Recent Literature, Arch. Dermat. & Syph. **18**:237 (Aug.) 1928. (*e*) Andrews, G. C.: Diseases of the Skin, ed. 2, Philadelphia, W. B. Saunders Company, 1938, p. 377. (*f*) Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943, p. 872.

6. (*a*) Gottron, H.: Gleichzeitiges Vorhandensein von Erythema induratum und Sarkoid Darier-Roussy, Dermat. Ztschr. **58**:39, 1930. (*b*) Volk, R.: Tuberkulose der Haut, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 10, pt. 1, p. 380. (*c*) Hämel, J., and Hoede, K.: Die Tuberkulosen der Haut, in Arzt, L., and Zieler, K.: Die Haut- und Geschlechtskrankheiten, Berlin, Urban & Schwarzenberg, 1934, vol. 3, p. 613. (*d*) Proppe, A.: Zur Frage des Darier-Roussyschen Sarkoids an Hand eines ungewöhnlichen Falles, Dermat. Ztschr. **72**:311, 1936.

7. Schaumann, J.: Sur quelques dermatoses non attribuables à la lymphogranulomatose bénigne, Bull. Soc. franç. de dermat. et syph. **41**:1322, 1934.

8. Beintema, K.: Classification des sarcoïdes hypodermiques, Bull. Soc. franç. de dermat. et syph. **41**:1367, 1934.

9. Pautrier, L. M.: Comment doit se poser la question des sarcoïdes, Bull. Soc. franç. de dermat. et syph. **41**:1002, 1934.

10. Maloney, E. R., and Combes, F. C.: Darier-Roussy's Sarcoid, with Special Reference to Its Tuberculous Etiology, Arch. Dermat. & Syph. **33**:709 (April) 1936.

11. Pinner, M.: Noncaseating Tuberculosis: Analysis of Literature, Am. Rev. Tuberc. **37**:690, 1938.

12. Greschebin, S.: Concerning the Identity of Sarcoid Boeck, Sarcoids Darier-Roussy, Erythema Induratum Bazin and Lupus Pernio, Urol. & Cutan. Rev. **39**:477, 1935.

losis, regarded Boeck's sarcoid, Darier-Roussy's sarcoid and erythema induratum as related lesions of tuberculous origin.

It is evident that different types of lesions have been described under the term Darier-Roussy's sarcoid. Some of the cases described undoubtedly represent sarcoidosis. This can be said with certainty of those cases in which the subcutaneous lesions occurred simultaneously with sarcoid lesions in the skin as well as other organs.[13] Histologically, the subcutaneous lesions in these cases showed the same structure as the cutaneous lesion. In some of the reported cases the number of giant cells was unusually large.[14] In others fibrosis was so pronounced that only a few cells remained.[15]

The cases reported as of Darier-Roussy's sarcoid in which subcutaneous nodes but no cutaneous or systemic lesions of sarcoidosis were present showed no uniform histologic picture. In practically none of these cases did the microscopic appearance resemble that of sarcoidosis, so that it may be stated that no incontestable case of sarcoidosis with subcutaneous lesions only is on record. Most, if not all, of these cases can be classified as either erythema induratum[16] or Weber-Christian disease.[17] It thus appears that the term Darier-Roussy's

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13. (*a*) Finnerud.[5a] (*b*) Barber.[5b] (*c*) Winkler, M.: Beitrag zur Frage der "Sarkoide" (Boeck), resp. der subkutanen nodulären Tuberkulide (Darier), Arch. f. Dermat. u. Syph. **77**:3, 1905. (*d*) Lenartowicz, J., and Rothfeld, J.: Ein Fall von Hautsarkoiden (Darier-Roussy) mit identischen Veränderungen im Gehirn und den inneren Organen, ibid. **161**:504, 1930. (*e*) Gougerot, H.; Burnier, and Eliascheff, O.: Tuberculose pernio du nez et tuberculoses "sarcoïdes" hypodermiques disséminées, Bull. Soc. franç. de dermat. et syph. **39**:218, 1932. (*f*) Nicolas, J.; Gaté, J.; Michel, P. J., and Tiran, P.: Lésions de la base du nez et des mains à type de "lupus pernio": Sarcoïdes noueuses disséminées sclérodermiformes, ibid. **39**:489, 1932. (*g*) Ducrey, C.: Sarcoid di Boeck e sarcoid ipodermico di Darier-Roussy in uno stesso sogetto: Contributo allo studio dei tuberculidi, Riv. di pat. e clin. d. tuberc. **6**:678, 1932. (*h*) Ernsting, H. C.: Boeck's Sarcoid of the Eyelid with Coexisting Darier-Roussy's Sarcoid: Report of a Case, with a Review of the Literature, Arch. Ophth. **17**:493 (March) 1937.

14. Gougerot, Burnier and Eliascheff.[13e] Ernsting.[13h]

15. Finnerud.[5a] Ernsting.[13h]

16. Darier and Roussy.[3a] Darier.[3b] Finnerud.[5a] Proppe.[6d] Volk, R.: Zur Kenntnis der "subkutanen Sarkoide" (Darier-Roussy), Wien. klin. Wchnschr. **26**: 1425, 1913. Nobl, G.: Zur Identität des subkutanen Sarkoid (Darier) mit dem indurativen Erythem (Bazin), Wien. med. Wchnschr. **63**:2342, 1913. Schaumann, J.: Étude sur le lupus pernio et ses rapports avec les sarcoïdes et la tuberculose, Ann. de dermat. et syph. **6**:357, 1917. Bertaccini: Observation sur un cas douteux: Erythème induré ou sarcoïdes hypodermiques, Bull. Soc. franç. de dermat. et syph. **41**:1362, 1934.

17. Maloney and Combes.[10] Pautrier, L. M., and Robert: Sarcoïdes hypodermiques à tendence atrophique de la face, Bull. Soc. franç. de dermat. et syph. **32**:119, 1925. Roederer, J., and Diss, A.: Sarcoïdes hypodermiques de type histologique anormal, ibid. **35**:75, 1928.

sarcoid should be discarded, or at least used only in a clinical descriptive sense.

Histologic Aspects.—The course of development of the lesions in this case appears to have been as follows: (1) Infiltration of the tissue with monocytes and lymphocytes—this type of infiltrate was seen in the erythrodermic lesions and in the form of small foci in the vicinity of the soft, subcutaneous nodes. (2) Focal transformation of monocytes into epithelioid and giant cells with early fibrosis—this was seen in the peripheral parts of the soft subcutaneous nodes. (3) Increasing fibrosis and giant cell formation together with progressive obliteration of cells of other types, a "healing" phase—this picture was observed in the center of the soft subcutaneous nodes and throughout the firm nodes.

The histologic picture presented by the firm nodes was not what is usually considered typical of sarcoidosis. Nevertheless, various features, such as the granulomatous pattern, the paucity or absence of lymphocytic infiltration within the lesions and the appearance of the reticulum, were considered sufficiently distinctive to warrant the diagnosis. In many respects the lesions closely resembled those described by Robb-Smith [18] as "giant cell reticulosis" (Stengel-Wolbach sclerosis). This lesion was first described by Stengel [19] (case 4) in 1904 and later by Wilson [20] and Kettle [21] (case 4) as a cause of splenomegaly. Robb-Smith stated that while it was most commonly seen in the spleen it could also occur as a generalized process throughout the lymphoid tissue and presented several rather vague points of differentiation from sarcoidosis. However, all the histologic criteria used by Robb-Smith as differential points—decided fibrosis, giant cells with asteroid inclusions, reticulum fibers encircling each cell and discrete cells in the granulomas—can be observed to a greater or lesser degree in unquestioned cases of sarcoidosis. Furthermore, it must be noted that it is only in recent years that splenomegaly has come to be recognized as a feature of sarcoidosis.[22] It seems likely that "giant-cell reticulosis" and "typical" sarcoidosis represent variants of the same pathologic process rather than separate entities.

Asteroid Bodies: A review of the literature reveals that asteroid inclusion bodies in giant cells have been described in at least 68 cases.

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18. Robb-Smith, A. H. T.: Reticulosis and Reticulosarcoma: A Histological Classification, J. Path. & Bact. **47**:457, 1938.

19. Stengel, A.: Varieties of Splenic Anemia, Tr. A. Am. Physicians **19**:174, 1904.

20. Wilson, L. B.: The Pathology of Splenomegaly: A Study of the Operative and Autopsy Material from the Mayo Clinic, Surg., Gynec. & Obst. **16**:240, 1913.

21. Kettle, E. H.: The Splenic Lesions in Some Cases of Splenomegaly Associated with Secondary Anemia, J. Path. & Bact. **23**:413, 1919-1920.

22. Friedman, M.: Sarcoidosis of the Spleen: Report of a Case with Autopsy and a Study of Intracellular "Asteroid Bodies," Am. J. Path. **20**:621, 1944.

Although several authors [23] had previously described them, Wolbach [24] and Vogel [25] were the first to study in detail their tinctorial behavior. Hirsch,[26] in 1935, reviewed the literature pertaining to asteroid bodies and collected 26 cases, to which he added 36 of his own. He failed to include the 3 cases reported by Winkler,[13c] Jadassohn [27] and Görl.[28] Since his report, 1 case each has been reported by Nickerson,[29] Friedman [22] and Skavlem and Ritterhoff.[30] The fact that Hirsch alone observed 36 cases suggests that the occurrence of asteroid bodies is commoner than the literature would indicate.

In 5 of the 68 cases the asteroid bodies occurred in the skin. The first case is that of Winkler,[13c] described in 1905. The patient had cutaneous and subcutaneous lesions of sarcoidosis, as well as sarcoidosis of the cervical and inguinal lymph nodes. Histologic examination of a cutaneous lesion revealed in some of the giant cells "spider-like or starlike figures." Herxheimer and Roth,[31] in a case of "lupus pernio" of the skin, observed in the giant cells crystalloid radial inclusions. Jadassohn,[27] in a case of "multiple superficial sarcoids" of the face, observed "asteroid bodies." He stated that he had seen them also in other cases of sarcoidosis. Diss [32] described asteroid bodies in the giant cells of a tumor, the size of a hazelnut, which had developed slowly without ulceration on the forehead of a woman aged 65. The tumor was composed of "inflammatory nodules formed by irregular masses of large giant cells intermingled with epithelioid cells." There was

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23. Winkler.[13c] Goldmann, E. E.: Eine ölhaltige Dermoidcyste mit Riesenzellen, Beitr. z. path. Anat. u. z. allg. Path. **7**:553, 1890. Ris, F.: Ein Fall von Cyste des grossen Netzes, Beitr. z. klin. Chir. **10**:423, 1893. De Buck, D., and Broeckaert, J.: A propos d'un paraffinome, Bull. Acad. roy. de méd. de Belgique **17**:890, 1903.

24. Wolbach, S. B.: A New Type of Cell Inclusion, Not Parasitic, Associated with Disseminated Granulomatous Lesions, J. M. Research **19**:243, 1911.

25. Vogel, K.: Ueber eigenartige Fremdkörperriesenzellen bei Bronchiolitis obliterans, Virchows Arch. f. path. Anat. **206**:157, 1911.

26. Hirsch, E. F.: Radial Inclusions of Gient Cells, Arch. Path. **20**:665 (Nov.) 1935.

27. Jadassohn, J.: Zur Frage der "Saroide," des Lupus pernio und des Lupus miliaris in Kombination mit "Acnitis," Cor.-Bl. f. schweiz. Aerzte **49**:455, 1919.

28. Görl, P.: Ein Beitrag zur Kasuistik des subkutanen Sarkoids Darier-Roussy, Arch. f. Dermat. u. Syph. **148**:130, 1924-1925.

29. Nickerson, D. A.: Boeck's Sarcoid: Report of Six Cases in Which Autopsies Were Made, Arch. Path. **24**:19 (July) 1937.

30. Skavlem, J. H., and Ritterhoff, R. J.: Coexistent Pulmonary Asbestosis and Sarcoidosis, Am. J. Path. **22**:493, 1946.

31. Herxheimer, G., and Roth, W.: Zur feineren Struktur und Genese der Epitheloidzellen und Riesenzellen des Tuberkels, Beitr. z. path. Anat. u. z. allg. Path. **61**:1, 1915-1916.

32. Diss, A.: Les corps astéroides dans les cellules géantes, Bull. et mém. Soc. anat. de Paris **94**:349, 1924.

no caseation or necrosis. In addition to asteroid bodies, there were doubly refractile crystals in some of the giant cells. Diss expressed the belief that the lesion represented a foreign body granuloma produced by the crystals. The histologic description would, however, suggest a diagnosis of sarcoidosis. Görl [28] described a case in which there were multiple subcutaneous nodes. Histologic examination of a node revealed it to be composed of numerous cysts filled with fat. In addition, there were numerous nodular inflammatory foci, in some of which giant cells containing asteroid bodies were present. The author regarded the case as one of Darier-Roussy's sarcoid. The histologic description does not allow a definite diagnosis, although nodular panniculitis (Weber-Christian disease) seems likeliest.

In the histologic sections which were obtained by biopsy from more than 70 patients with sarcoidosis and examined at the Pathologic Laboratory of the Massachusetts General Hospital, asteroid bodies were observed in 10 additional cases, including 3 of sarcoidosis of the skin. Asteroid bodies have also been observed in occasional foreign body giant cells seen in routine material examined in this laboratory. These observations, together with those in the 68 reported cases make it evident that these bodies are most commonly seen in foreign body giant cells and in the giant cells of sarcoidosis.[33] They have also been described in the giant cells of other granulomas, including at least 1 case of torulosis,[34] 1 of leprosy [35] and 1 probable case of Weber-Christian disease.[28] In a considerable number of the reported cases the cause of the granulomatous process could not be determined with certainty. The asteroid bodies appear to represent nonspecific cytoplasmic inclusions the nature of which is still obscure, although Hirsch [26] concluded from his experiments with animals that they represented crystallized fat. It seems certain that these inclusions have no diagnostic significance.

SUMMARY AND CONCLUSIONS

An unusual case of sarcoidosis presented extensive erythrodermic lesions and large subcutaneous nodes.

The subcutaneous nodes had the clinical appearance of Darier-Roussy's sarcoid. Since different types of lesions have been described as Darier-Roussy's sarcoid, including subcutaneous sarcoidosis, erythema induratum and Weber-Christian disease, the term should be discarded or used only in a clinical descriptive sense.

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33. Winkler.[13c] Friedman.[22] Jadassohn.[27] Nickerson. [29] Skavlem and Ritterhoff.[30] Herxheimer and Roth.[31]

34. Stoddard, J. L., and Cutler, E. C.: Torula Infection in Man, Monograph 16, Rockefeller Institute for Medical Research, 1916, p. 55.

35. Mallory, F. B.: The Principles of Pathologic Histology, Philadelphia, W. B. Saunders Company, 1914, pp. 207 and 613.

Histologic examination of the nodes showed considerable fibrosis surrounding islands of epithelioid and giant cells. Many of the giant cells contained asteroid inclusion bodies. The picture was consistent with that described as giant cell reticulosis (Stengel-Wolbach sclerosis). It is believed that giant cell reticulosis and "typical" sarcoidosis represent variants of the same pathologic process.

The nature of asteroid bodies is still obscure. They are most commonly observed in the giant cells of foreign body granulomas and of sarcoidosis. It seems certain that they have no special diagnostic significance.

TREATMENT OF DERMATOLOGIC LESIONS BY PARAVERTEBRAL SYMPATHETIC GANGLION BLOCK

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IN A STUDY of the susceptibility of the postphlebitic extremity to allergic lesions [1] it was observed that cutaneous lesions in such extremities, in some patients, improved rapidly or were completely cleared up following lumbar paravertebral sympathetic ganglion block with procaine hydrochloride. Experience with the effect of sympathetic ganglion block with procaine hydrochloride on certain cutaneous lesions in the extremities, with and without a history of thrombophlebitis, is the subject of this report. In 15 of 25 patients with postphlebitic chronic cutaneous lesions of the extremities and ulcers of the phlebitic chronic cutaneous lesions of the extremities and ulcers of the leg and in 3 of 5 patients with similar lesions without past phlebitis improvement or healing was affected with this type of treatment. In many of the patients in whom healing was effected the lesions had been present for years and had proved intractable to other treatment.

The exact mechanism operating in the improvement of these lesions is not known. However, sympathetic ganglion block with procaine hydrochloride was done with the thought that the block would break up a vicious cycle, initiated by the previously damaged segment of vein, which was causing reflex vasomotor phenomena, such as vasopasm and increased sweating in some patients and vasodilatation in others.[1a] In other words, one appeared to be dealing with a minor causalgia. Treatment of the causalgic state with regional sympathetic ganglion block resulted in improvement or healing of postphlebitic dermatitis and ulcers.

Because of the improvement obtained in a number of postphlebitic dermatologic diseases that had resisted other types of treatment, stubborn types of dermatitis, similar to postphlebitic lesions, in the feet and legs of patients who had no evidence of any venous disease, have also been

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1. Naide, M.: Allergic Lesions Following Thrombophlebitis, Arch. Int. Med. **80**:388 (Sept.) 1947.

1a. Homans, J.: Vasomotor and Other Reactions to Injuries and Venous Thrombosis (Trimble Lecture), Am. J. M. Sc. **205**:313 (March) 1943.

treated. An example of this type of dermatitis treated by paravertebral ganglion block is reported in case 3.

Lumbar paravertebral sympathetic block was done by injection of 10 to 15 cc. of 1 per cent procaine hydrochloride in the region of the first lumbar sympathetic ganglion and, in most patients, a similar amount of procaine hydrochloride into the second lumbar sympathetic ganglion. The method for doing a paravertebral block has been described in numerous publications.[2] A successful block was indicated by a rise in temperature of the foot and absence of sweating on the side where the injection was given. A successful block was often accompanied with relief of pain or tenderness in a lesion. Improvement in cutaneous lesions has been observed following one block. However, at least three and up to six blocks are necessary in many patients.

In 2 patients, lumbar sympathectomy was done following temporary improvement with a block using procaine hydrochloride. The disease in 1 of these patients has been healed for three months. The other had a recurrence of the dermatitis three weeks postoperatively, following the development of recurrent superficial thrombophlebitis.

Several examples of dermatologic disease in patients with and without a history of thrombophlebitis are herein reported.

REPORT OF CASES

CASE 1.—F. M., a white man 48 years old, was seen in November 1944 with a history of bilateral thrombophlebitis following pneumonia in October 1943. He presented ulceration in the left leg with severe pruritus. Examination revealed the left ankle to be swollen, with dry dermatitis and pigmentation of the left leg and decided tenderness over the involved area (fig. 1). The skin of the left leg was distinctly more moist than that of the right. The pulses were normal. Oscillometric readings were equal in both ankles. This patient had three paravertebral blocks, with considerable relief of pain and swelling but with some residual edema. The dermatitis was improved, but not completely. He was fairly comfortable until two months later, when he returned with recurrence of pain and oozing of the skin on the left leg. Again, a lumbar paravertebral block on the left side was done, but this time there was no rise in temperature, so that it is questionable as to whether the block was effective. He obtained no relief from this and did not return again until July 1945, when three ulcers were present and associated with a great deal of pain. This time two blocks were done, with healing of two of the ulcers within two weeks and improvement of the third ulcer. The latter ulcer healed shortly after this visit. When seen again in April 1946 the skin was still in good condition, although pigmented.

CASE 2.—S. S., a white woman 50 years old, presented a history of severe pain in the right ankle, of five months' duration. The ankle was red and tender. A cast had been applied, with formation of an ulcer on the right lateral malleolus. She

2. Ochsner, A., and DeBakey, M.: Thrombophlebitis: Role of Vasospasm in Production of Clinical Manifestations, J. A. M. A. **114**:117 (Jan. 13) 1940. Burns, Shock, Wound Healing and Vascular Injuries, prepared under the auspices of the Committee on Surgery, National Research Council, Division of Medical Sciences, Philadelphia, W. B. Saunders Company, 1943.

had had a great deal of treatment, including the use of elastic bandages, rubber stockings and roentgen rays, with persistence of the ulcer. Examination revealed a pigmented area 2 by 8 cm. with a small ulcer 3 by 10 mm. deep, but with a clean base, over the right external malleolus. This ulcer was tender. There were a number of small dilated veins on both calves. A paravertebral block on the right side was done, with relief of the pain. The symptom, however, recurred, so that she required hospitalization again, with relief of pain following caudal anesthesia, which was done because this type of anesthesia could be prolonged for four hours as contrasted with the one hour of anesthesia produced by paravertebral block with procaine hydrochloride. The lesion on the right leg and

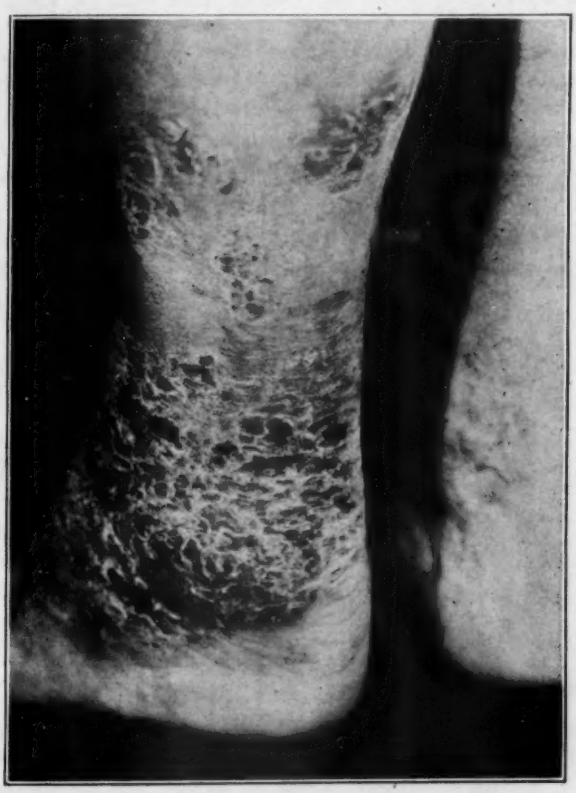

Fig. 1 (case 1).—Postphlebitic dermatitis or "eczema." Increased sweat on the left leg is suggestive of sympathetic stimulation as part of a causalgic state.

severe pain recurred a number of times, with relief of pain only with caudal anesthesia or paravertebral block. On one occasion heparin was used, because of the presence of thrombosed veins above the ulcerated area (fig. 2). The patient remained well until there apparently developed generalized pruritus and dermatitis due to an unknown allergen. First, severe pruritus developed over the inner aspect of the right leg where there were several thrombosed veins. Two weeks later severe itching and papules developed on both forearms and cubital spaces. This illustrates how permanent relief of postphlebitic disease in an extremity will not occur until the offending allergen is eliminated.

CASE 3.—M. K., a white woman aged 64, gave a history of moist dermatitis on the distal portion of the left foot for the past eight years. The left foot had seemed colder than the right, subjectively. The disease was accompanied with a good deal of pruritus and some swelling. She smoked eight to ten cigarets a day, and there was no history of diabetes mellitus. Examination revealed moist dermatitis of the left toes and distal portion of the left foot, proximal to the fifth toe. The left foot was definitely edematous, and there was increased pressure in the veins on the left leg when she stood. However, there was no obvious venous incompetence and no evidence of phlebitis, so that the increased pressure in the veins may have been due to increased flow of blood in the left foot as the result of local inflammation. The left foot was slightly colder and sweated more than the right. All pulses were palpable in both legs and oscillometric readings were normal, suggesting that the arterial circulation was adequate. Knee and ankle jerks were present, but vibration sense was absent in the toes of the left foot. The results of the rest of the physical examination were essentially negative. Because there were

Fig. 2 (case 2).—Postphlebitic dermatitis and ulceration in the left leg, with palpable thrombosed veins encircled. The left leg presents no phlebitis and no dermatitis.

several objective signs of a possible element of causalgia, including a lower temperature and increased sweating of the left foot, it was decided to try several lumbar sympathetic blocks with procaine hydrochloride. Following the first block, within a week, there was definite improvement in the dermatitis, and after another block the patient reported the dermatitis had improved a great deal and was better than it had ever been. There was still scale formation, but, as the patient put it, she no longer had the heavy crust forming on the dermatitis. Her condition was definitely improved.

COMMENT

The exact mechanism operating in these patients is unknown. A possible explanation is that as a result of blocking of veins mechanically

or by venospasm, allergens or bacteria, which would normally not produce any symptoms, accumulate in sufficient concentration to produce a clinical condition.[1] Another possibility is that as the result of even slight inflammation of the skin, possibly due to the fungi that cause dermatophytosis or bacterial inflammation, there has been damage to nerve endings in the skin which set up minor causalgia. The important point is that something similar to minor causalgia may be set up by inflammation, which is certainly a form of trauma, which may be a factor in the prolonged persistence of some cutaneous diseases. Minor causalgia might be defined simply as a focus or area of irritability in damaged nerve endings or nerve fibers in the skin and subcutaneous tissue, or in blood vessel walls, which results in the production by reflex efferent stimuli of various phenomena, such as increased local sweating or vasoconstriction. This vicious cycle may persist until procaine hydrochloride is injected into the sympathetic ganglions. Following this temporary interruption, the reflex may not reestablish itself after the effect of the procaine hydrochloride wears off. Abnormal chemical formation, either quantitative or qualitative, may take place at nerve endings or neuromuscular junctions in causalgic states, which may account for persistence of some dermatologic diseases despite all types of treatment. Nomland [3] pointed out diseases such as cholinogenic urticaria and cholinogenic itching which he was able to reproduce in 4 patients with acetylbetamethylcholine.

If a patient has had generalized allergic dermatitis, which is severer on the previously phlebitic extremity, then that type of lesion is much less likely to respond to paravertebral block than the lesion that is limited to this extremity. In these patients, the concentration of the allergen, or the sensitivity, is so great that dermatitis would have appeared in the previously phlebitic leg even had there not been any past phlebitis. Elimination of allergens is obviously indicated when the offending allergen is known.

SUMMARY AND CONCLUSIONS

The treatment and relief of some chronic types of dermatitis by paravertebral sympathetic ganglion block with procaine hydrochloride is reported. Complete healing or improvement occurred in 18 of 30 patients. Twenty-five of these patients had chronic cutaneous lesions or ulcers in extremities which had in the past been phlebitic. Sympathectomy may be necessary in some patients.

The possibility that minor causalgia may be a factor in the persistence of some chronic dermatologic diseases is discussed.

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3. Nomland, R.: Cholinogenic Urticaria and Cholinogenic Itching, Arch. Dermat. & Syph. **50**:247 (Oct.) 1944.

PATCH TESTS VERSUS USAGE TESTS

With Special Reference to Volatile Ingredients

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WHILE the "prophetic patch test," as published by Schwartz and Peck,[1] has come into frequent use in determining the sensitizing potency of materials and chemicals coming in contact with the skin, unless it is carried out properly erroneous conclusions may be reached. It seems to us that this point is not sufficiently stressed, as is exemplified in a recent article by Underwood and his associates.[2] Schwartz and Peck,[3] in their "Cosmetics and Dermatitis," repeatedly stressed the fact that usage tests are often necessary in order to check and interpret the reactions obtained in patch tests, especially when dealing with certain types of chemical substances and compounds.

While patch tests give a fairly accurate idea of the relative cutaneous irritating and sensitizing properties of a new formula placed on the market, they do not always give an accurate idea of what may happen under conditions of actual use. The factors which are especially important as regards their interpretation in the patch test are those volatile ingredients which the preparations contain. In the patch test the concentration of volatile solutions is much higher than in actual usage as far as the level of their concentration and the duration which that concentration acts on the skin are concerned.

In this study the propionate compounds were used, because these preparations have been widely used and little, if any, dermatitis has been reported from their application. They have also been accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

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1. Schwartz, L., and Peck, S.: The Patch Test in Contact Dermatitis, Pub. Health Rep. **59**:546 (April 28) 1944.

2. Underwood, G. B., and others: Overtreatment Dermatitis of the Feet, J. A. M. A. **130**:249 (Feb. 2) 1946.

3. Schwartz, L., and Peck, S.: Cosmetics and Dermatitis, New York, Paul B. Hoeber, Inc., 1946.

EXPERIMENTAL PROCEDURE

For the purpose of the experiment, the technic of the so-called "prophetic patch test" was used on more than 200 patients. In this procedure, a routine patch test is made, the substance is left on for twenty-four hours and reactions, if any, are observed at twenty-four and forty-eight hours subsequent to the test. After two weeks the patch test is repeated in the same patient, and reactions are observed twenty-four and seventy-two hours later (table).

The first series of patch tests will, if the patient has never been exposed to any of the ingredients used in the test, indicate whether there will be a reaction of primary irritation. The second series of

Results of Patch Tests and Usage Tests with "Sopronol" Ointment and Ingredients

	Tests for Primary Irritant					Tests for Sensitization					Usage Tests on Positive Reactors				
		Reactions *					Reactions *					Reactions *			
Substance	Number	0	1+	2+	3+	Number	0	1+	2+	3+	Total No.	0	1+	2+	3+
"Sopronol" ointment	204	186	15	1	2	193	190	3	0	0	21	0	0	0	0
3.6% propionic acid solution, aqueous	211	207	4	0	0	196	193	1	2	0	7	0	0	0	0
16.4% sodium propionate solution, aqueous	211	208	2	1	0	196	194	1	1	0	5	0	0	0	0
"Sopronol" base	214	213	1	0	0	193	191	2	0	0	3	0	0	0	0
"Sopronol" powder	205	190	15	0	0	191	189	2	0	0	17	0	0	0	0

* Key: 1+ = erythema; 2+ = papule; 3+ = vesicle; 4+ = ulceration.

patch tests will give, if reactions are present, the number that were sensitized by the first application.

In these patch tests, "sopronol" ointment and powder were used and the actual concentration of the individual active ingredients as they are found in the powder and ointment. "Sopronol" powder consists of:

	Gm. or Cc.
Calcium propionate	15.0
Zinc propionate	5.0
Talc	80.0

"Sopronol" ointment consists of:

Sodium propionate	16.4
Propionic acid	3.6
Propylene glycol	5.0
N-propyl alcohol	10.0
Zinc stearate	5.0
"Carbowax"	35.0
Water, sufficient to make	100.0

RESULTS

According to the routine interpretation of the results of the patch test, as is indicated in the table, the "sopronol" ointment and all of its active ingredients produced some primary irritation, since as far as is known none of these patients had ever used this preparation previously. In the second series the interpretation would be different. A number of patients exhibiting so-called reactions of primary irritation in the first series did not show any reactions in the second. If a primary irritant is being employed, the reactions of primary irritation should be reproducible. Those that did not show a reaction in the first series and exhibited a reaction in the second application might be regarded as having been sensitized.

It can be seen that the reactions were irregular and difficult to evaluate. The clue to the inconsistency of the results with the patch test was readily discernible when all of the reactors were given usage tests by daily application for a period of one week with the ingredients to which they showed reactions. This was usually the ointment, since in all instances those that reacted to the individual ingredients and the powder reacted to the ointment. It should be noted that in no instance did dermatitis develop in any of the reactors under conditions of the usage test.

Schwartz and Peck stated:[3]

> Before a new formula is placed on the market, closed patch tests should be performed by a competent dermatologist on at least 200 subjects with the new formula, using as a control an old formula which has been on the market for years, and which has caused no unusual number of complaints. The closed patches should remain on for forty-eight hours after which the reactions should be read each day for three days in order to observe late reactions. The number of reactions obtained from the new formula should not exceed the number obtained from the old.
>
> Ten days after the last reading of the reactions, new closed patches of both new and old formulas should be applied on the same 200 subjects and allowed to remain for forty-eight hours and the reactions again read each day for three days after removal of the patches. If the number of subjects showing sensitization reactions from the new formula exceeds the number showing sensitization reactions from the old one, the formula is unsafe. These tests will give an idea of the relative skin-irritating and sensitizing properties of the new formula as compared with the old one, but they do not give an accurate idea of what may happen under conditions of actual use. Therefore, the following additional tests should be performed:
>
> The same 200 people should actually use the old and the new cosmetic each day on opposite sides of the body for a period of four weeks. No cases of dermatitis should result from the old cosmetic. If no cases of dermatitis result from the new formula, it is safe to place it on trial sale. If only one case results, then another group of 200 people should be subjected to the actual use test, and if one or more cases of irritation occur in this group, then the product should be discarded as unsafe. If no cases occur in the second group of 200, the remainder of the tests . . . may be given in the cosmetic. . . .

By trial sale is meant the sale for a period of not less than one month . . . (if no cases of dermatitis are reported before this time) . . . in one community; between 5,000 and 10,000 packages of the cosmetic should be sold. . . . If no cases of dermatitis are reported during the trial sale, the cosmetic may be put on the market.

If any cases of dermatitis are reported during the trial sale, the manufacturer should engage the help of a competent dermatologist to investigate them and to determine the actual cause. The continued sale of the cosmetic or its withdrawal from the market should depend on such an investigation.

In trying to ascertain whether a cosmetic or a pharmaceutic product is the cause of dermatitis, it is better to apply the cosmetic daily to the same site of skin for at least four days, in the manner in which the cosmetic is actually used rather than in the form of a patch test, because cosmetics are not covered when used and usually a large part of the volatile ingredients, such as perfumes, disappears from the skin by evaporation. Covered patch tests do not permit such evaporation, and many cosmetics or pharmaceutic products which are harmless in actual use may elicit positive reactions in patch tests when applied with a covered patch.

In preparations such as "sopronol" ointment and powder, the active ingredients are long chain fatty acids of the saturated type. These are volatile, and in the covered patch tests evaporation was not possible. An irritation resulted which was not duplicated under the conditions of actual use.

CONCLUSIONS

Routine patch tests should not be carried out indiscriminately with chemical substances or compounds, such as pharmaceutic or cosmetic preparations, without a thorough evaluation of the physical and chemical properties of the active ingredients. This is especially true when dealing with volatile substances, such as are found in many of these preparations. In dealing with a preparation the physical and chemical properties of which are unknown, it is best to carry out actual usage tests to determine the sensitizing potency. This may be necessary to supplement the routine patch test procedure.

PARA-ANTHRAX

Infection with Organisms Resembling Bacillus Anthracis

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THE TYPICAL clinical features of anthrax constitute one of the medical classics appreciated by every student. However, it is not generally realized that bizarre manifestations may result from infection with organisms closely resembling Bacillus anthracis. The case reported herein was discussed with a number of outstanding clinicians in this area. In no instance was anthrax suggested as a diagnostic possibility.

Probably such cases should be grouped under the term para-anthrax. Such a classification could include all atypical cases due to anthrax-like bacilli. It should be emphasized that para-anthrax differs significantly from true anthrax. These variations are apparent both clinically and bacteriologically. However, many of the features so closely mimic anthrax that the relation between the two entities should be reflected in the name.

REPORT OF A CASE

F. M. S., a 15 year old white school girl, was referred to me on Dec. 1, 1945. She stated that she had been scratched on the left wrist by a stray cat three months previously. About one week later a small papule developed in the area of the scratch, which slowly healed without significant treatment. Two weeks before examination a large mass developed in her left epitrochlear region, and a few days later a similar swelling appeared in her left axilla. At about the same time she noted a daily rise in temperature, reaching 103 F. (oral). This had slowly subsided, so that by December 1, she had only an afternoon rise to 99.5 F. daily. She had taken 20 tablets of sulfadiazine, 0.5 Gm. each, about one week prior to examination, without benefit. The patient presented massive lymphadenopathy involving her left epitrochlear and axillary regions. The glands were firm and mildly tender. The overlying skin was not discolored. There was no evidence of fluctuation. There was a healed ecthymatous lesion on her left wrist. There were no masses felt in her breasts. The other lymph nodes were not enlarged. The liver and spleen were not palpable. The results of the remainder of the examination were negative.

Laboratory Observations.—The observations in two urinalyses were not remarkable. A blood cell count was done on December 11, with the following results: the hemoglobin was 15.3 Gm. (90 per cent), the erythrocyte count was 4,720,000 per cubic millimeter and the color index was 0.95. The white blood cell count was 11,000 per cubic millimeter, with 72 per cent polymorphonuclear leukocytes, of which 24 were stab forms and 48 were segmented, 1 per cent eosinophils and

27 per cent lymphocytes. The red blood cells were grossly normal. The cell count was repeated six days later, with similar observations. The white blood cell count was now 12,400 per cubic millimeter, with 74 per cent polymorphonuclear leukocytes; 20 of these cells were stab forms, the other 54 being segmented. There were also 19 per cent lymphocytes, 1 per cent monocytes, 3 per cent eosinophils and 3 per cent basophils.

The reactions in Kolmer, Kahn and Kline tests were negative. Reactions in serologic tests for tularemia were negative in dilutions of 1 to 20 through 1 to 1,280 on December 1 and again on December 13. The sedimentation rate was rapid. By the Linzenmeier method there was a fall of 18 mm. in twenty-one minutes. The Cutler method of study gave the following results:

10 min	3 mm.	40 min	24 mm.
20 min	16 mm.	50 min	25 mm.
30 min	22 mm.	60 min	25 mm.

Reactions in intradermal tests with old tuberculin (strengths 1 and 2) histoplasmin, coccidioidin and Frei antigen were negative.

Histologic studies of excised tissue from the epitrochlear and axillary glands revealed inflammatory and necrotic changes. The germinal centers were hyperplastic and edematous. The capsule was acutely inflamed. In some areas a large zone of necrosis could be seen. This was composed of cellular debris and amorphous eosinophilic material. Fibrosis was prominent near the periphery of these necrotic areas. There were no giant cells noted. There was no evidence of a lymphoblastomatous process.

Bacteriologic Studies.—Material was obtained at operation under sterile precautions from both the epitrochlear and the axillary areas. No bacteria were noted on stained slides made from this material. Acid-fast stains were negative. Potassium hydroxide preparations failed to reveal the presence of any fungi. Cultures in simple broth showed no growth after twenty-four hours, but in forty-eight hours a pure culture of a large rod was observed.[1] It grew satisfactorily in anaerobic cultures. There was no growth on Sabouraud's medium.

The organism was observed to be a gram-positive large slender rod growing singly and in chains of varying length. It was definitely motile. The ends were rounded. There was no capsule noted. Spores formed both equatorially and subterminally. Studies showed it to be an aerobe with facultative anaerobic characteristics. It produced acid, but no gas, in glucose, sucrose and maltose. Growth in broth resulted in slight turbidity and formation of sediment. In milk, an alkaline reaction was produced without clotting. On a gelatin stab, slow liquefaction resulted, with the surface membrane adhering to the sides of the tube. The rod produced beta type hemolysis on blood agar. There was slight liquefaction of blood serum.

It was felt that from these characteristics the organism could best be classified as Bacillus anthracoides.

Treatment and Course.—The patient was hospitalized from December 10 to 24. Among the therapeutic measures tried, without benefit, were penicillin, given intramuscularly in doses of 25,000 units every three hours for a total dose of 1,400,000 units, sulfadiazine, 1 Gm. every four hours for a total of 70 Gm., roent-

1. The organism was isolated by Dr. William W. Reich and his staff at the Herrick Hospital, but the final identification was made by Dr. Paul Michael and his staff at Peralta Hospital, Oakland.

gen rays, at 120 kilovolts filtered through 3 mm. of aluminum for a total dose of 185 r, infra-red radiation and hot compresses.

On December 19 it was decided to explore the axillary mass. Dr. Maurice Zeff performed a biopsy and observed the outer portion of the gland to be firm, but the central portion was necrotic. The organism described previously was isolated from the central area. Three days later the epitrochlear mass became fluctuant, and it was removed on December 22. At operation the node was seen to be necrotic and the capsule destroyed. It was necessary to remove the gland piecemeal.

While in the hospital, the patient had an intermittent afternoon fever, the temperature rising as high as 100.4 F. (oral). By December 13 the peaks had

Bacteriologic Features of Bacillus Anthracoides, Bacillus Anthracis and Bacillus Subtilis

	B. Anthracoides	B. Anthracis	B. Subtilis
Structure	Large slender rod forming short chains	Large slender rod forming short chains	Large slender rod forming long chains
Ends	Rounded	Square	Rounded or square
Capsule	None	Present	None
Gram stain	Positive	Positive	Positive
Motility	Present	None	Present
Spores	Equatorial, subterminal	Equatorial	Equatorial, subterminal
Metabolism	Aerobe, facultative anaerobe	Aerobe, facultative anaerobe	Aerobe, facultative anaerobe
Glucose, sucrose, maltose	Acid, no gas	Acid, no gas	Acid, no gas
Gelatin stab	Slow liquefaction, with surface membrane adhering to sides of tube	Slow liquefaction, grows into gelatin (inverted fir tree)	Rapid liquefaction, with surface membrane adhering to sides of tube
Broth	Slight turbidity and sediment	No turbidity or sediment	Moderate turbidity and sediment
Milk	No clotting, alkaline	Slow coagulation, alkaline	Alkaline, no coagulation
Blood agar	Beta type hemolysis	Little, slow hemolysis	Beta type hemolysis
Blood serum	Slight hemolysis	Little hemolysis	Hemolysis
Pathogenicity (man)	Severe	Severe	Mild
Main involvement	Lymph nodes	Skin	Eye
Response to penicillin and sulfonamide drugs	None (1 case)	Good	.....

dropped to 99.6 F. After the second operation the temperature became normal. After this recovery was uneventful and complete. All signs of inflammation had completely subsided by Jan. 20, 1946.

BACTERIOLOGIC CONSIDERATIONS

The accompanying table outlines the differentiating bacteriologic features of B. anthracoides, B. anthracis and Bacillus subtilis. From the table, it is easier to see the points of resemblance than to appreciate the differentiating features. Briefly, B. anthracoides is separated from B. anthracis by its lack of capsule, the rounded ends, the motility and the different type of growth in gelatin.

Variations in B. anthracis have been described frequently. Heaslip [2] described 40 cases of anthrax-like infection that he collected from the literature. The clinical features were dissimilar to classic anthrax and to each other. He discussed the possibility of their being due to variations in the anthrax bacillus with the production of an atypical picture.

However, these are probably different organisms, closely related to B. anthracis.

CLINICAL CONSIDERATIONS

The mildness and evanescence of the cutaneous symptoms (i. e., the original cat scratch) make this disease entirely different from the gangrenous edematous forms of cutaneous anthrax. Lymphadenopathy is the rule in anthrax, but in this case the lymph node involvement completely overshadowed the cutaneous and systemic features. It was this that masked the anthrax-like nature of the disease. The necrosis of the glands without suppuration was an interesting observation.

If one can judge from the published reports, the failure of this patient to respond to treatment with sulfonamide drugs and penicillin is at variance with the usual observations in anthrax. The clinical picture presented in this case is not pathognomonic. In fact, I treated a patient with the identical appearance and course following a cat scratch at the same time that F. M. S. was being observed. In this case, however, only Streptococcus viridans and Staphylococcus aureus could be cultured.

The pathogenicity of B. subtilis in man seems to be limited to the eye. The virulence of B. anthracis and B. anthracoides is far greater than is that of B. subtilis.

Therefore, this report is offered to acquaint clinicians with this anthrax-like disease due to B. anthracoides. This case suggests that surgical intervention is the treatment of choice.

SUMMARY

A case of an infection due to Bacillus anthracoides following a cat scratch is reported.

The infection involved the lymph nodes, with the cutaneous symptoms being insignificant.

Surgical intervention proved curative after the failure of treatment with penicillin, sulfonamide drugs and roentgen rays.

The differentiating features between anthrax and para-anthrax are briefly outlined.

1904 Franklin Street.

2. Heaslip, W. G.: Bacillus Tropicus, a New Species Isolated from Man and Animals Described and Compared with Other Bacilli Resembling Bacillus Anthracis, M. J. Australia **2**:536 (Nov. 8) 1941.

PAGET'S DISEASE OF THE VULVA

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THE CLINICAL picture that Paget [1] described in 1874 as a disease of the mammary areola preceding cancer of the mammary gland was soon known to have not only characteristic clinical features but also a peculiar microscopic picture, which entitled it to be classified in a separate group of cutaneous epitheliomatoses.

When it was observed that similar pathologic changes could be diagnosed in regions of the skin other than the mammary areola, there began a prolonged controversy as to the precise nature and site of origin of Paget's disease and its peculiar cells (to which the term Paget's cells has been applied), which still persists.

The disease is rare. The nipple is the commonest site; women are more commonly affected than men. However, among the 33 published cases of extramammary Paget's disease, 14 have been described as affecting the external genital organs; only 8 cases have been accepted, as far as can be ascertained, in which the vulva was the site of the disease.

Weiner,[2] in a recent critical review of Paget's disease, stated that many cases with extramammary sites recorded in the literature must be discounted either on the basis of insufficient published evidence or because the lesions belong to classes which can be grouped as melanoma with intradermal spread (Stout [3]), adenocarcinoma (Sekiguchi [4] and Civatte [5]),

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From the New York Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, Columbia University.

1. Paget, J.: On Disease of the Mammary Areola Preceding Cancer of the Mammary Gland, St. Barth. Hosp. Rep. **10**:87-89, 1874.

2. Weiner, H. A.: Paget's Disease of the Skin and Its Relation to Carcinoma of the Apocrine Sweat Glands, Am. J. Cancer **31**:373-403 (Nov.) 1937.

3. Stout, A. P.: The Relationship of Malignant Amelanotic Melanoma (Naevocarcinoma) to Extramammary Paget's Disease, Am. J. Cancer **33**:196-203 (June) 1938.

4. Sekiguchi, S., and Tashiro, O.: Paget's Disease of the Nipple, Mitt. a. d. path. Inst. d. k. Univ. zu Sendai **1**:385-392, 1919-1921.

5. Civatte, A.: Un cas de maladie de Paget de l'aisselle avec cancer, Bull. Assoc. franç. p. l'étude du cancer **17**:297-314 (May) 1928.

squamous cell carcinoma (Matzenauer [6]), basal cell carcinoma (Potter [7] and Trimble [8]), Bowen's disease (Ormsby [9]) or as other distinctly carcinomatous eruptions. Such controversial terminology results from the diversity of hypotheses as to the nature of Paget's disease.

At present it is doubtful whether all authors who refer to Paget's disease actually are dealing with the same entity. Doubtless many pathologic changes which are different from each other exhibit the same clinical signs and have, therefore, been grouped as one disease. Accordingly, each case must be classified on its own merits and observations.

REPORT OF A CASE

Z. F., a woman 66 years of age, had a husband and three sons living. She had never been seriously ill. In 1941 the patient complained of an itching eruption on the vulva, for which she was treated by different physicians with various ointments and, at one time, with four weekly doses of 75 r unfiltered to the vulva; no improvement was noted. After consultation in the office the patient was admitted to the New York Skin and Cancer Unit on Dec. 9, 1942. At that time she was a well nourished woman who showed no clinical signs other than an eruption of remarkable appearance. It was a definitely demarcated intensely reddish purple lesion extending over the labia majora and involving a great deal of the hairy region of the mons veneris. The labia were diffusely swollen, and the affected area was thickened and spongy. The surfaces of the visible part of the labia majora were moist and edematous, but were not hard. There was no ulceration, but there were some wartlike excrescences on the ventral margin and small isolated areas of white sodden-looking epithelium on the inner surfaces of the labia. The introitus of the vagina and the vaginal mucosa showed smooth glistening senile atrophic mucosal changes and were not perceptibly thickened. The vagina was normal; the cervix was small and showed a little clear mucoid excretion.

The inguinal lymph nodes could hardly be felt and were not unusually enlarged, considering the area and the duration of the eruption. The femoral lymph nodes were not palpable. No nodes or tumor masses could be felt on gynecologic examination. Dilatation and curettage a few months previously had shown the uterus to be normal.

Treatment consisted of 100,000 units of vitamin A three times daily and 50 mg. testosterone three times a week for one month. No change was noted in the clinical appearance or in the microscopic picture of a biopsy specimen taken after this treatment. From June 14, 1943, six roentgen ray treatments were given to the vulva at intervals of four days; each dose consisted of 550 r filtered through 3 mm. of aluminum.

The lesion did not change in size or elevation, but showed more oozing than before; the itching, according to the patient, was "still unbearable." The patient

6. Matzenauer, R.: Paget's Disease, Monatschr. f. prakt. Dermat. **35**:205-125 (Sept.) 1902.

7. Potter, J.: Extra-Mammary Paget's Disease, J. Cutan. Dis. **34**:306-307 (April) 1916.

8. Trimble, W. B.: Paget's Disease of the Abdomen, Arch. Dermat. & Syph. **7**:665-666 (May) 1923.

9. Ormsby, O.: Superficial Epitheliomatosis (Paget's), J. Cutan. Dis. **33**: 391 (May) 1915.

was sent to the department of gynecology for vulvectomy, but she refused the operation.

In 1944 and 1945, when the patient was seen only once a year (while I was in the Army), the lesion did not change clinically.

During the last year of her life, the patient showed evidences of senility, childishness, occasional mental confusion and uncleanliness; she was admitted to the psychiatric ward of Bellevue Hospital and died there on Jan. 1, 1946. Autopsy revealed that the immediate cause of death was general and cerebral arteriosclerosis; arteriosclerotic cardiac disease was a contributory cause, and, among other diseases described, chronic atrophic vulvitis (Paget's disease?) was involved.

Fig. 1.—Clinical picture of Paget's disease of the vulva.

Three biopsies were made at different times from different parts of the lesion, before and after treatment with hormones and roentgen rays had been instituted.

Microscopic Diagnosis.—Dr. Else A. Barthel gave the following report of the biopsy:

The epidermis in part of the section was relatively normal except where the growth began. There the rete pegs were long and varied much in size and shape. They were filled with islands of atypical prickle cells. The nuclei were hyperchromatic, and the cells varied in size and shape as well as affinity for eosin. Occasionally they had broken through the epidermal borders and the normal con-

tours of the basal cells had disappeared, so that they persisted in some places as a thin line. These atypical cells, however, had not invaded the corium. The reaction in the corium was limited to the papillary bodies. The blood vessels were filled with blood cells, and cellular exudate surrounded them. The endothelial cells were swollen and showed toxic changes. There were large pigmented

Fig. 2.—Low power general view of the surface epidermis, with the transition from normal skin to the affected area. There are no Paget cells in the cutis or appendages.

Fig. 3.—The surface epidermis at greater magnification, with the epidermopapillary line completely intact and the barrier of lymphoid and plasma cells beneath it.

nuclei, which probably were connective tissue nuclei. There were occasional plasma cells, and some of the nuclei showed granular degeneration. There did not seem to be any single tumor cells present.

The epidermis in another part of the section was normal, and in the other part the rete pegs were exaggerated. Scattered throughout the rete pegs were islands of atypical prickle cells, separated from the surrounding closer to normal epithelium by zones of lysis. In other areas of the epidermis there was a washing out of the normal prickle cell contours, so that they showed a homogeneous acid stain. In these areas there were shadow nuclei. The surface was covered by a parakeratotic scale that was occasionally nonparakeratotic. The blood vessels in the corium were dilated and in several places ruptured. There was a large amount of edema in the papillary bodies and upper part of the corium. Cellular exudate consisted of round cells and plasma cells. These showed toxic changes. Endothelial cells in the blood vessels were not especially affected in this area. There was no evidence of any cellular infiltration of the growth in the corium.

The diagnosis was Paget's disease.

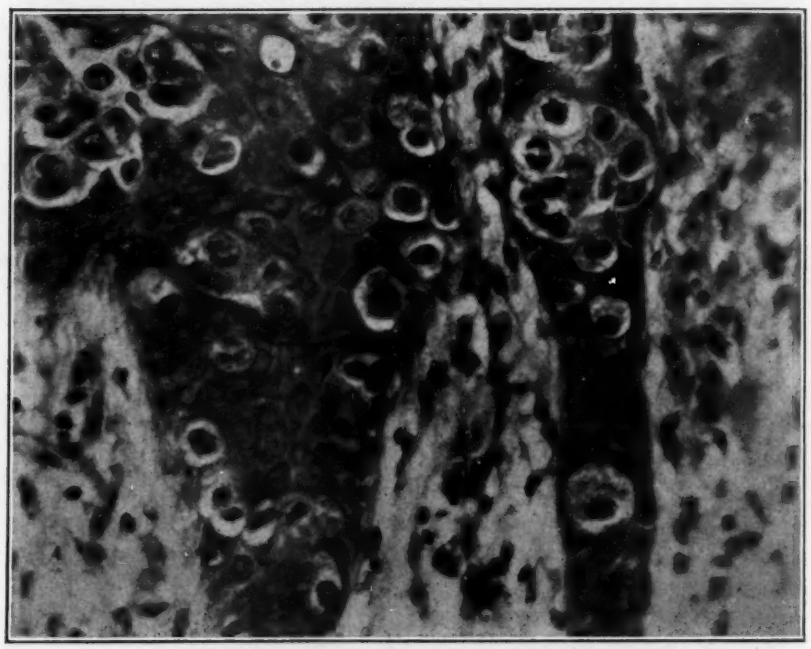

Fig. 4.—Characteristic Paget cells at greater magnification.

When this case was presented before the New York Dermatological Society,[10] there was general agreement among the physicians discussing the case that extramammary Paget's disease does exist and that this case appears to fit the picture presented by the disease.

An almost identical case of vulvar involvement is being prepared for publication in the *American Journal of Gynecology and Obstetrics* by H. P. Wager. His patient, aged 71, came to the Rectal Clinic of the Post-Graduate Hospital for the first time eleven years ago, with a small

10. Traub, E. F.: Paget's Disease of the Vulva, Arch. Dermat. & Syph. **48**: 559-560 (Nov.) 1943.

Paget's eruption of the perianal region. A local excision was performed in 1935. However, the lesion recurred and spread to the fourchet and the labia majora. In 1945 a total vulvectomy was done. No clinical evidence of other carcinomatous growth was seen. As in the case herein reported, the histologic examination showed the characteristic features in the epidermis but no evidence of pagetoid involvements in the deeper structures.

Although it would be easiest to accept Weiner's conclusions on the basis of observations in his case that Paget's disease is a carcinoma of glandular orign, it would lead to the supposition of Fraser,[11] who stated the belief that "there is strong evidence that the so-called extramammary Paget's disease is Bowen's disease" and, furthermore, that the diagnosis "Bowen's disease," according to Wile's discussion of Fraser's paper,[12] should be omitted from future textbooks altogether as a misnomer.

As convincing as Weiner's argument seems to be, and as tempting as it is to try to bring all cases of Paget's disease, mammary and extramammary, under one heading, a well characterized clinical and microscopic entity, if used only for teaching purposes, would consequently be thrown into the conglomerate class, "carcinoma," which is so loosely used by some, even for benign and obviously nonmetastasizing tumors. On the other hand, it would not solve the question: precancerosis or cancer? Nor would it explain those cases in which underlying primary carcinoma could not be observed; and enough cases have been described in the literature by reputable and serious observers to warrant the supposition that they do exist. How, then, should one classify the disease in such cases? Does one find an explanation in the histogenesis of the Paget cell? The two main points of the discussion cannot be separated: Is the Paget cell malignant from the beginning, and where does it originate?

After discarding his theory of the infectious "psorosperm," Darier [13] himself postulated that the Paget cell is the result of "faulty development of the epidermis and imperfect keratinization in the malpighian layer" and classed it as "dyskeratosis." He does not use the term "precancerosis," but speaks of "preepithelioma."

Arnd [14] expressed the view that Paget's disease is precancerosis. He proved his point by staining with Best's carmine, by which he demon-

11. Fraser, J. F.: Bowen's Disease and Paget's Disease of the Nipple, Arch. Dermat. & Syph. **18**:809-828 (Dec.) 1928.

12. Wile, U., in discussion on Fraser.[11]

13. Darier, J.: (*a*) Note sur l'anatomie pathologique de la maladie dite "Psorospermose folliculaire végétante," à propos d'un cas nouveau, Ann. de dermat. et syph. **7**:742-747, 1896; (*b*) Le cancer de la dermatose précancéreuse de Bowen, ibid. **1**:49-61, 1920.

14. Arnd, W.: Ueber die Pagetsche Erkrankung der Brustwarze, Virchows Arch. f. path. Anat. **261**:700-731, 1926.

strated that the Paget cells are epithelial cells rich in glycogen and that developmental transitions could be observed between normal prickle cells and glycogen-filled Paget cells, which are neither autochthonous carcinoma cells nor metastatically transported into the surface epithelium. The production of glycogen is not a sign of degeneration. Such cells can develop multicentrically in the epidermis, the appendages and the milk ducts.

Hannemüller and Landois [15] suggested that the Paget cells are epidermal cells, swollen through osmosis, while Handley [16] expressed the belief that the changes are nutritional and nonmalignant.

An opposite view was held by Jacobaeus,[17] who stated the belief that the Paget cells are cancer cells from the beginnng but secondary to, or metastatic from, an underlying glandular carcinoma. This opinion was adopted by Ribbert,[18] MacKee and Cipollaro [19] and Weiner, while other authors [20] rejected it.

Cheatle,[21] for example, offered another explanation, which he based on the study of serial sections taken through the whole mammary gland. He claimed that Paget's disease can be caused by changes in the epidermis alone and that the formation of Paget's cells may or may not be accompanied with the intraepidermic invasion of neoplastic cells from below. In other words, it is a constitutional disease produced by a common agent which, independently, causes the epidermic changes and may produce simultaneously the cancerous changes below. A similar opinion was offered by Kyrle [22] in 1907.

Muir [23] looked on Paget's disease of the nipple as an "intraduct carcinoma" with a low degree of malignancy. He contended that the

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15. Hannemüller, K., and Landois, F.: Paget's Disease of the Nipple, Beitr. z. klin. Chir. **60**:296-312, 1908.

16. Handley, S.: Non-Malignant Diseases of the Breast and Their Relation to Mammary Cancer, Brit. M. J. **1**:309 (Feb. 11) 1911.

17. Jacobaeus, H. C.: Paget's disease und sein Verhältnis zum Milchdrüsenkarzinom, Virchows Arch. f. path. Anat. **178**:124-142, 1904.

18. Ribbert, H.: Ueber den Pagetkrebs, Deutsche med. Wchnschr. **31**:1218-1220 (Aug. 3) 1905.

19. MacKee, G. M., and Cipollaro, A. C.: Cutaneous Cancer and Precancer, New York, American Journal of Cancer, 1937, p. 158.

20. Zieler, K.: Ueber die sogenannte Pagetsche Krankheit und die intraepidermoidale Krebsausbreitung, Dermat. Wchnschr. **101**:1441-1445 (Nov. 16) 1935.

21. (*a*) Cheatle, G. L.: Paget's Disease of the Nipple, Brit. J. Surg. **12**:284-288 (Oct.) 1924. (*b*) Cheatle, G. L., and Cutler, M.: Tumours of the Breast: Their Pathology, Symptoms, Diagnosis, and Treatment, Philadelphia, J. B. Lippincott Company, 1931, p. 336.

22. Kyrle, J.: Drüsenkrebs der Mamma unter dem klinischen Bilde von Paget's Disease, Arch. f. Dermat. u. Syph. **83**:187-202, 1907.

23. Muir, R.: Paget's Disease of the Nipple and Its Relationships, J. Path. & Bact. **30**:451-471, 1927.

Paget cell may arise in "multiple foci." He defined the Paget cell as a cancer cell growing within a healthy, or at least non-neoplastic, epithelium. In his cases there were always changes in the duct epithelium.

Ewing,[24] while not committing himself to a definite statement of histogenesis, expressed the belief that the disease occurs in two forms: one in which no tumor of the breast is present and the prognosis is favorable and the other in which there is a rapidly growing carcinoma of the breast, probably arising from the ducts and spreading to the thoracic wall and skin, in which the prognosis is unfavorable. Ewing, to whom I showed my patient and the slides from the biopsies, agreed with the diagnosis and suggested treatment with roentgen rays.[25]

Arzt and Kren [26] made a similar distinction. They described 4 cases, among 16 cases studied, in which underlying carcinoma could not be established. They accepted for the larger group the theory of Jacobaeus that the primary change which takes place is the glandular carcinoma and that Paget's disease of the areola represents a special kind of metastasis. However, they themselves asked why, considering the frequency of the metastatic process in mammary carcinoma, the clinical and anatomic picture of Paget's disease so rarely results.

Four cases, in which no underlying carcinoma was demonstrable, remained, however, and for these they had to accept a second explanation (even though it must be comparatively rare in the ratio of 1 to 4); they therefore concluded that such Paget cells cannot be metastatic carcinoma cells but must originate locally from the rete. They termed the disease in these cases "precancerous."

The hypothesis that the Paget cell has a multicentric origin has gained credence ever since Kyrle in 1907 postulated that "the histogenesis of the clearly defined clinical diagnosis cannot be found in a common pathologic-anatomic denominator," since in one case the basal cell and in another a cylindric cell or glandular carcinoma may produce the clinical picture, either the surface epithelial cells of the areola or the covering epithelial cells of the lactiferous ducts being the source of the "carcinom-matrix."

These and similar suggestions and theories have been brought forth because so many authors could not classify their cases under "a common denominator," since no underlying carcinoma could be detected which could be made responsible for the "skin metastasis"; some even refused to accept in their cases the presence of cancer.

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24. Ewing, J. A.: Neoplastic Diseases: A Treatise on Tumors, ed. 4, Philadelphia, W. B. Saunders Company, 1940, p. 900.

25. Personal communication to the author.

26. Arzt, L., and Kren, O.: Die Paget's Disease mit besonderer Berücksichtigung ihrer Pathogenese, Arch. f. Dermat. u. Syph. **148**:284-312, 1925.

Dörffel and Grimm (1935) [27] published a new case of extramammillary Paget's disease of the vulva, which even Weiner accepted as typical of Paget's disease and in which no evidence of carcinoma could be observed. The Paget cells originated "in the epidermis and did not migrate into it from below." That, they said, does not exclude the possibility that in other cases Paget's disease might originate secondarily from a glandular carcinoma. Observations speak for that fact. However, they accepted the viewpoint of Gans [28] that one should not argue "either or," but "as well as." For purely didactic reason they proposed: (1) morbus Paget simplex—the Paget cell is produced within the epidermis, and the disease is precancerous and (2) morbus Paget metastaticus—Paget's disease is a secondary cutaneous carcinoma, i. e., a metastasis by continuity.

Drake and Whitfield [29] described another case in which the disease was located in the vulva, which, in their opinion, proved definitely that the characteristic changes of Paget's disease originate in more than one place.

Although they had not seen a break-through of the affected hair follicle, sweat duct and sweat gland and the only invasion into the fibrous tissue took place from the surface epithelium downward, as shown by the extensive downgrowth of the papilla with no bursting through the basal cell margin, the term "precancerous" seemed objectionable to them. They claimed that it was an indolent form of carcinoma.

COMMENT

Paget's disease rarely occurs in parts of the body other than the nipple. The fact that it does occur in extramammary sites, however, has been used as an argument in favor of the hypothesis that it is a primary disease of epidermal origin. Even the proponents of this hypothesis have not concluded whether the disease is precancerosis or cancer. A case like Weiner's, in which a direct continuity could be proved between masses of an epidermal tumor of the vulva through the lymph nodes into the abdominal cavity, affecting the uterus and ovary (or vice versa) and in which even a group of cells in a metastatic nodule in the rib resembled Paget's cells, would support the assumption that the cutaneous manifestation is a metastasis of an adenocarcinoma.

Even though in the majority of cases of the mammillary type a direct continuity between underlying carcinoma and the epidermal lesion

27. Dörffel, J., and Grimm, O.: Beitrag zur Histogenese des Morbus Paget, Dermat. Wchnschr. **101**:1169-1173 (Sept. 21) 1935.

28. Gans, O.: Histologie der Hautkrankheiten, Berlin, Julius Springer, 1925, vol. 2, p. 360.

29. Drake, J. A., and Whitfield, A.: Paget's Disease of the Vulva, Brit. J. Dermat. **41**:177-187 (May) 1929.

has been reported, the objection of Cheatle and Cutler that such a carcinoma could just as well grow downward from the epidermis cannot be discounted. The question as to which comes first, the tumor below or the cutaneous eruption above, is difficult to answer, since in a number of cases no underlying tumor is seen.

In order to ascertain where my case fits, it may be argued that, although the classic epidermal changes but no underlying tumor from which the Paget cell could have been transported into the surface epithelium or a breakthrough past the basal cell membrane into the subcutis can be seen, the disease might start in the ducts of the apocrine glands and Paget's cells might originate at any point, high up in the epidermis at the syringeal pore of a sudoriferous gland of the breast or wherever apocrine glands exist. One must otherwise go to the extent of suggesting two different forms of the disease: a status simplex of epidermal origin and a status metastaticus of glandular origin.

From the duration of the controversy, it can be seen that a critical observation has not been made. Most investigators have judged their cases on the basis of slides of 5 microns. I am fully conscious that in that direction data in my own case are likewise incomplete. The purpose of adding another case is to emphasize the need for proper observation that must entail serial sections of the entire lesion. What might be accomplished by such an arduous task, besides reaffirming the existence of extramammary Paget's disease, is simply to establish in each case whether a subepidermal carcinoma is present or not. Even then one would not be able to generalize on 1 case only, just as any statement regarding the histogenesis of the Paget cell would be a matter of speculation. However, if a number of such cases were studied in this manner, a conclusion may be arrived at between the three possibilities:

1. All cases of Paget's disease start in the epidermis.

2. All cases start in the apocrine gland or its duct.

3. They can start both in the epidermis and in the apocrine gland, either simultaneously or successively. In this case, Paget's disease could be a tumor of multilocular origin. This concept would tend to reconcile many of the divergent opinions as to the points of origin of the Paget cell.[30]

Classification is of didactic and clinical value only. From the dermatologic point of view, it would be regrettable to eliminate the present

30. Dr. Marion B. Sulzberger, in discussing the latter possibility, pointed out that while this hypothesis cannot be proved either there is much supported evidence for this idea of origin in both the mammary gland and the epidermis. This would coincide well with the common embryologic origin of the epithelial structures of the mammary gland and the skin.

concept of Paget's disease of extramammary or mammary location and classify all cases alike as the mastastases of adenocarcinomas. The rarity of intraepidermic metastasis from cancer makes even pathologists doubt the validity of such generalization, just as it makes them doubt the existence of an epidermotropic factor as the carcinogenic agent of the Paget cell.

The opinion expressed by von Recklinghausen in 1875 that "staining reactions of dead tissues are insufficient evidence on which to base biologic generalizations" is true today, as it was then.

SUMMARY

The ninth case of extramammary Paget's disease of the vulva is reported.

The nature and origin of Paget's disease of the skin are discussed.

Until the time when pathologists can set up exact biologic experiments to determine the starting point of a tumor cell, any statement as to the histogenesis of the Paget cell would be a matter of mere speculation. The conception of the multilocular origin is the most plausible.

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PATHOGENESIS OF BENIGN TUMORS OF CUTANEOUS APPENDAGES AND OF BASAL CELL EPITHELIOMA

I. Benign Tumors of the Cutaneous Appendages

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THE PATHOGENESIS of basal cell epithelioma has so far not been satisfactorily determined. In this communication, an attempt is made to show that basal cell epitheliomas are not carcinomas but related to the so-called benign epitheliomas, cutaneous adenomas and nevi organomatosi. Evidence will be presented that the tumors belonging to these four groups are nevoid tumors, or hamartomas, originating, in accordance with the Cohnheim theory, from arrested embryonal cells, in this instance from cells of the primary epithelial germ. Variations in the degree and in the direction of differentiation prior to the onset of neoplasia would explain adequately the wide variety of histologic pictures presented. A classification of the tumors originating from the primary epithelial germ will be presented, following which the various types of tumors included in this classification will be discussed.

DEVELOPMENT OF THE EPIDERMIS

Since my intention is to show that the tumors which are the subject of this presentation originate from the primary epithelial germ, an embryonal structure, a short review of the development of the epidermis seems indicated. Two sets of structures eventuate from the embryonal stratum germinativum, the pavement epithelium and the cutaneous appendages [1] (fig. 1).

The pavement epithelium in early fetal life consists of the embryonal stratum germinativum and the periderm or epitrichial layer. The latter disappears, but the former persists and during late fetal life differentiates into the basal cell layer from which the squamous epithelium develops. Basal cells possess intercellular bridges [2] and form cells with intercellular bridges.

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Dr. Tracy B. Mallory and Dr. Benjamin Castleman, Boston, and Dr. Fred D. Weidman, Philadelphia, gave advice and made valuable suggestions.

1. Pinkus, F.: Die normale Anatomie der Haut, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol. 1, pt. 1, pp. 87 and 116.

(Footnotes continued on next page)

The cutaneous appendages develop from two types of cells which begin to differentiate in the embryonal stratum germinativum during the third and fourth month: the eccrine sweat gland germ cells and the primary epithelial germ cells. They possess no intercellular bridges and form cells without intercellular bridges. The eccrine sweat gland germ cells give rise to the eccrine sweat glands, the primary epithelial germ cells to the hair matrix, sebaceous glands and apocrine glands. Only the hair and its two internal sheaths develop from the hair matrix. The outer sheath of the hair, or hair follicle, and the duct of the sebaceous gland are composed of prickle cells and originate from cells with the potentiality of forming prickle cells, namely, basal cells.

The term primary epithelial germ (primärer Epithelkeim) was introduced by Marks.[3] Investigating the development of the skin in domestic animals, he observed that in hairy parts their sweat glands

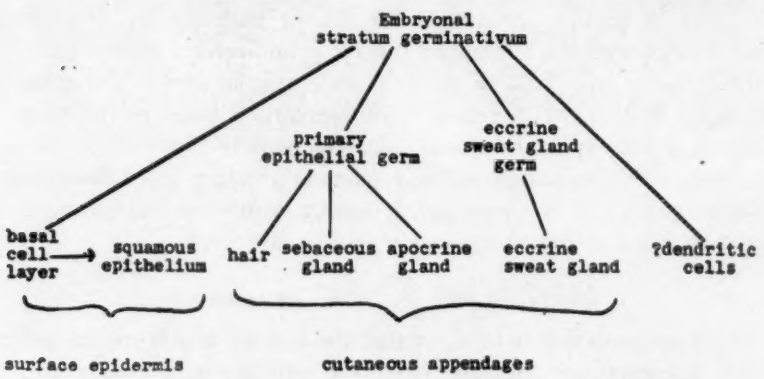

Fig. 1.—Diagram of the development of the epidermis.

originate from the hair germs. In order to denote that in these animals the hair germ has the potentiality to form sebaceous and sweat glands as well as hair, he suggested the term primary epithelial germ in place

2. (*a*) Pinkus.[1] (*b*) Hoepke, H.: Die Haut, in von Möllendorf, W.: Handbuch der mikroskopischen Anatomie des Menschen, ibid., 1927, vol. 3, pt. 1, pp. 4 and 77. (*c*) Haythorn, S. R.: Studies on the Histogenesis of the So-Called "Basal Cell Carcinoma," Am. J. Cancer **15**:1969, 1931. (*d*) Beck, S. C.: Epithelioma, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1933, vol. 12, pt. 3, p. 254. (*e*) Pernkopf, E., and Patzelt, V.: Anatomie und Histologie der Haut, in Arzt, L., and Zieler, K.: Die Haut- und Geschlechtskrankheiten, Berlin, Urban & Schwarzenberg, 1934, vol. 1, p. 33. (*f*) Montgomery, H.: Histogenesis of Basal Cell Epithelioma, Radiology **25**:8 1935.

3. Marks, P.: Untersuchung über die Entwicklung der Haut, insbesondere der Haar- und Drüsenanlagen bei den Haussäugetieren, Inaug. Dissert., Berlin, W. Buxenstein, 1895.

of hair germ. Römer [4] confirmed Marks' observations. Schiefferdecker [5] first recognized that two types of sweat glands exist in mammals, those which develop from the primary epithelial germ and those which develop "directly from the epidermis." He observed that sweat glands originating from the primary epithelial germ possess large lumens and that their secretory cells pass through a full cycle of secretory stages. They are low cylindric at the beginning of the cycle, gradually increase in height until they protrude far into the lumen and then release part of their cytoplasm into the lumen. Schiefferdecker chose the name apocrine for these glands, because part of the cytoplasm of their cells is pushed off ("apo"). In contrast, he noted that the sweat glands originating "directly from the epidermis" possess smaller lumens and that their cells do not change their size or shape and do not release any cellular material into the lumen. He called these glands eccrine, because their cells simply excrete ("ec").

In man eccrine glands are present everywhere in the skin, while apocrine glands are encountered in only a few areas, namely, in the axillas, around the nipples, in the perigenital and perianal regions and, as modified glands, in the external auditory canal (ceruminal glands), in the eyelids (Moll's glands) and in the breast (mammary glands). Occasionally, a few apocrine glands are seen on the abdomen and chest. Schiefferdecker [5] noted, however, that in other areas, during embryonal life, apocrine glands begin to form with the hair and sebaceous glands, but disappear before full development.

One other type of cell which is found in the epidermis may be mentioned, the dendritic cell. The question whether the dendritic cell is epidermal or neural in origin has not yet been settled. The occasional presence of dendritic cells in basal cell epithelioma is one of the reasons for Bloch's belief [6] that they are epidermal in origin. If so, the dendritic cell would represent an additional type of cell developing from the embryonal stratum germinativum (fig. 1).

PATHOGENESIS OF EPIDERMAL TUMORS

On the basis of these embryologic considerations the epithelial tumors of the skin may be divided into two groups, namely, tumors of the surface epidermis and tumors of the cutaneous appendages. In each group nevoid tumors, or hamartomas, and carcinomas occur.

4. Römer, F.: Studien über das Integument der Säugetiere: II. Das Integument der Monotremen, Denkschr. d. med. naturw. Gesellsch. **6**:189, 1898.

5. Schiefferdecker, P.: Die Hautdrüsen des Menschen und der Säugetiere, ihre biologische und rassenanatomische Bedeutung, sowie die Muscularis sexualis, Biol. Centralbl. **37**:534, 1917; Stuttgart, C. Scheizerbert, 1922.

6. Bloch, B.: Ueber benigne, nicht naevoide Melanoepitheliome der Haut nebst Bemerkungen über das Wesen und die Genese der Dendritenzellen, Arch. f. Dermat. u. Syph. **153**:20, 1927.

Nevoid tumors, or hamartomas, are defined as benign neoplasms which develop, in accordance with the Cohnheim theory, from arrested embryonal cells. Carcinomas are malignant neoplasms believed to arise, according to Hansemann's theory,[7] from "anaplastic" cells. Anaplastic cells are dedifferentiated cells which behave differently from embryonal cells. They are autonomous, able to exist more independently than embryonal cells and, therefore, survive when carried away through the lymphatic vessels and multiply as metastases. Carcinomas usually arise from mature cells, but embryonal cells may also change into anaplastic cells and thus give rise to a carcinoma, as, for instance, in branchiogenic carcinoma.

Tumors of the Surface Epidermis.—The nevoid tumors, or hamartomas, of this group are the papillomas (nevi verrucosi) which originate from embryonal basal cells and squamous cells. The carcinomas of this group are the squamous cell carcinomas which originate from mature basal cells and squamous cells due to their change into anaplastic cells. Since squamous cells develop from basal cells, squamous cell carcinoma represents a true carcinoma of basal cells.

Tumors of the Cutaneous Appendages.—The nevoid tumors, or hamartomas, of this group are the nevi organomatosi, the cutaneous adenomas, the benign epitheliomas and the basal cell epitheliomas. It is may belief that most of the tumors belonging to these four groups develop from primary epithelial germ cells, but some of them may develop from eccrine sweat gland germ cells. The carcinomas of the cutaneous appendages are the sebaceous gland carcinomas, eccrine gland carcinomas and apocrine gland carcinomas. They originate, as a rule, from mature cells of the cutaneous appendages and are rare. Many cases described in the literature as instances of carcinoma of sebaceous glands or sweat glands are, in my opinion, basal cell epitheliomas with differentiation toward sebaceous gland or apocrine gland structures and, as such, are not carcinomas.

CLASSIFICATION OF THE PRIMARY EPITHELIAL GERM TUMORS

The theory that the primary epithelial germ may give rise to tumors has so far found little consideration in the literature. Fischer[8] expressed the belief that syringoma and epithelioma adenoides cysticum develop from the primary epithelial germ, and Koch[9] and Pautrier[10]

7. Hansemann, D.: Ueber asymmetrische Zelltheilung in Epithelkrebsen und deren biologische Bedeutung, Virchows Arch. f. path. Anat. **119**:299, 1890.

8. Fischer, H.: Zur Genese epithelialer Hauttumoren, Dermat. Wchnschr. **83**:1509, 1926.

9. Koch, F.: Ueber das Vorkommen von apokrinen Drüsen in Talgnaevi. Arch. f. Dermat. u. Syph. **174**:126, 1936.

10. Pautrier, L. M.: Le naevus sébacé de la face et du cuir chevelu; l'épithelioma sébacé, Ann. de dermat. et syph. **7**:897, 1936.

stated the belief that nevus sebaceus (Jadassohn) develops from the primary epithelial germ. It is my belief that many other cutaneous tumors take their origin from it.

The following classification of the primary epithelial germ tumors, devised with the aid of Dr. Fred D. Weidman, is proposed. According to the decreasing degree of organization and differentiation, the primary epithelial germ tumors may be divided into four groups: organic tumors (nevi organomatosi), organoid tumors (adenomas), suborganoid tumors (benign epitheliomas) and nonorganic tumors (basal cell epitheliomas). I believe that the nevi organomatosi, the adenomas and the benign epitheliomas arise from primary epithelial germ cells which, prior to the onset of neoplasia, attained a certain degree of differentiation,

Classification of the Primary Epithelial Germ Tumors According to the Degree and the Direction of Differentiation

Primary Epithelial Germ Tumors	With Sebaceous Differentiation	With Apocrine Differentiation	With Hair Differentiation
Organic hamartomas (nevi organomatosi)	Sebaceous nevi 1. Nevus sebaceus (Jadassohn) 2. Adenoma sebaceum (Pringle)	Apocrine nevi	Hair nevi (including some cases of adenoma sebaceum [Pringle])
Organoid hamartomas (adenomas)	Sebaceous adenoma	Apocrine adenomas 1. Syringocystadenoma papilliferum 2. Hidradenoma papilliferum	
Suborganoid hamartomas (benign epitheliomas)	Sebaceous epithelioma	Apocrine epitheliomas 1. Syringoma 2. Cylindroma 3. Myoepithelioma	Trichoepithelioma (epithelioma adenoides cysticum)
Nonorganic hamartomas (*a*) Differentiated basal cell epitheliomas (*b*) Undifferentiated basal cell epitheliomas	Cystic basal cell epithelioma	Adenoid basal cell epithelioma	Keratotic basal cell epithelioma .....

whereas the basal cell epitheliomas arise from primary epithelial germ cells which attained no, or only little, differentiation. In each of these four groups the direction of differentiation can be toward sebaceous gland, apocrine gland or hair structures. Because tumors in transitional stages of differentiation are not infrequent and combinations of two or more varieties of primary epithelial germ tumors may occur in the same lesion, a great number of atypical tumors are encountered among the primary epithelial germ tumors. The positions which various cutaneous tumors occupy in the four groups are indicated in the table. The nomenclature follows that of Jadassohn.[11]

Some of the terms used to designate groups of tumors require definition.

11. Jadassohn, J.: Die benignen Epitheliome, Arch. f. Dermat. u. Syph. **117:** 577, 705 and 833, 1913-1914.

Nevus.—The term nevus is used in the literature in two different ways, referring either to a tumor composed of nevus cells (nevocellular nevus, pigmented nevus) or to a lesion originating from embryonal cells and composed of mature or nearly mature structures (organic nevi, "nevi organomatosi," e. g., nevus vasculosus, nevus sebaceus, nevus pilosus, nevus verrucosus). I suggest that, in order to avoid confusion, the term nevus when referring to an organic nevus be always used with a qualifying adjective, so that nevus without a qualifying adjective designates a tumor composed of nevus cells. In agreement with Werner and Jadassohn [12] I regard the organic nevi as tumors. Jadassohn and Werner stated that, since the organic nevi develop on the basis of an abnormal germ anlage and not by an increase in the size or number of mature structures, they were tumors and not hyperplasia.

Nevoid Tumor (Hamartoma).—Nevoid tumors, or hamartomas, are benign tumors originating, in accordance with the Cohnheim theory, from arrested embryonal cells. The choice of a satisfactory term for these tumors is difficult. Jadassohn [11] suggested that the term nevus be extended to include all of these tumors, not only those with mature or nearly mature structures ("nevi organomatosi") but also those with immature structures ("nevi adenomatosi," "nevi epitheliomatosi"). I believe, however, that this is inadvisable. The term nevus is already used as designation of two types of tumors, namely, nevocellular (pigmented) nevi and organic nevi. To give it still a third meaning would result in confusion. The term nevoid tumor appears more acceptable but lacks conciseness. Since an exact name for this large group of tumors is desirable, the suggestion is made that the term hamartoma be used. The term hamartoma, derived from the Greek word *hamartanein* (fail, miss, err), was coined by Albrecht [13] as designation of "tumor-like malformations showing a faulty mixture of the normal components of the organ in which they occur." He enumerated as examples cavernoma of the liver and spleen, tuberous fibroma of the renal medulla, tubular adenoma of the liver and pericanalicular and intracanalicular fibroma of the mamma. He further suggested that the term hamartoma be used not only for tumor-like malformations, which he thought may themselves be regarded as tumors, but also for the majority of benign tumors, such as neurofibroma, lipoma, hidradenoma and neuroglioma. On the basis of this suggestion, van der Valk [14] defined hamartomas as benign tumors of embryonal

12. Werner, A., and Jadassohn, J.: Zur Kenntnis der "systematisierten Naevi," Arch. f. Dermat. u. Syph. **33**:341, 1895.

13. Albrecht, E.: Ueber Hamartome, Verhandl, d. deutsch. path. Gesellsch. **7**:153, 1904.

14. van der Valk, J. W.: Adénome sébacé ou épitheliome sébacé primaire, Bull. Assoc. franç. p. l'étude du cancer **13**:465, 1924.

origin with an organoid structure. Since no satisfactory term exists for the entire group of benign tumors of embryonal origin, I suggest that the meaning of the term hamartoma be extended to include all such tumors, even those with suborganoid and nonorganic structure. Thus, the tumors arising from primary epithelial germ cells may be divided into organic hamartomas (nevi organomatosi), organoid hamartomas (adenomas), suborganoid hamartomas (benign epitheliomas) and nonorganic hamartomas (basal cell epitheliomas).

Epithelioma.—Epithelioma is a tumor of the epithelium (epidermis). The term epithelioma is used by many authors as a synonym for carcinoma of the epidermis. Since, however, the true meaning of the word is tumor of the epithelium, I believe that it may be used, as suggested by Jadassohn,[11] as designation of benign as well as of malignant tumors of the epidermis, provided that a qualifying adjective is added. I concur with Becker [15] that it would be ideal if the term epithelioma would be reserved for benign epidermal tumors and carcinoma be used for malignant epidermal tumors.

ORGANIC HAMARTOMAS (NEVI ORGANOMATOSI)

Nevi organomatosi originate from primary epithelial germ cells which, prior to the onset of neoplasia, attained such a high degree of differentiation that the resulting tumors are composed of mature or nearly mature organic structures. Since the primary epithelial germ gives rise to the sebaceous glands, apocrine glands and hair, sebaceous, apocrine and hair nevi belong in this group.

Sebaceous Nevi.—Two types occur, nevus sebaceus (Jadassohn) and adenoma sebaceum (Pringle).

Nevus Sebaceus: Nevus sebaceus is composed of large numbers of mature, or nearly mature, sebaceous glands. Frequently, apocrine glands and hair are also present.

Large glandular lumens have often been described as occurring in nevus sebaceus. Older authors [16] regarded them as dilated sweat glands.

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15. Becker, S. W.: Benign Epidermal Neoplasms, Arch. Dermat. & Syph. **26**:838 (Nov.) 1932.

16. (*a*) Foerster, A.: Atlas der mikroskopischen pathologischen Anatomie, Leipzig, Leopold Voss, 1854-1859, table 23. (*b*) Pollitzer, S.: A Case of Adenoma Sebaceum, J. Cutan. & Genito-Urin. Dis. **11**:475, 1893. (*c*) Wolters, M.: Ueber einen Fall von Naevus epitheliomatosus sebaceus capitis, Arch. f. Dermat. u. Syph. **101**:197, 1910. (*d*) Frieboes, W.: Ueber einen Fall von Naevus epitheliomatosus sebaceus capitis, Dermat. Ztschr. **22**:313, 1915. (*e*) Ostrowski, S.: Beitrag zur Histologie des naevus (epitheliomatosus) sebaceus unilateralis capitis, Acta dermat.-venereol. **8**:255, 1927. (*f*) Woolhandler, H. W., and Becker, S. W.: Adenoma of Sebaceous Glands (Adenoma Sebaceum), with Considerations of Keratotic Adenoma Sebaceum and True Adenoma of Sebaceous Glands, Arch. Dermat. & Syph. **45**:734 (April) 1942.

However, since Schiefferdecker's description of the apocrine glands in 1923,[5] most observers[17] have interpreted them as apocrine glands because of their size, their occasional connections with hair follicles and the active participation of the glandular cells in the process of secretion. Koch[9] and Pautrier[10] stated the belief that, because of the frequent presence of apocrine glands, nevus sebaceus develops from primary epithelial germs. Abortive hair follicles have also been observed in lesions of nevus sebaceus.[18] The presence of a basal cell epithelioma within a nevus sebaceus appears to be a rather frequent occurrence.[19]

Because several specimens of nevus sebaceus studied at the Massachusetts General Hospital showed apocrine glands (fig. 2) and abortive hair follicles, I believe, in accordance with Koch[9] and Pautrier,[10] that nevus sebaceus originates from primary epithelial germ cells. The occasional combination of nevus sebaceus and basal cell epithelioma may be regarded as evidence that both originate from primary epithelial germ cells.

Adenoma Sebaceum (Pringle): Adenoma sebaceum (Pringle) usually represents only part of a widely disseminated tissue malformation which results in the formation of tumors in both ectodermic and mesodermic structures.

Recent authors[20] are in agreement that adenoma sebaceum is a misnomer.

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17. (*a*) Koch.[9] (*b*) Pautrier.[10] (*c*) Balog, P.: Beitrag zur Frage des Schweissdrüsennaevus, Dermat. Wchnschr. **82**:841, 926. (*d*) Dietel, F.: Drüsennaevi, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1932, vol. 12, pt. 2, p. 630. (*e*) Robinson, S. S.: Naevus Sebaceus (Jadassohn), Arch. Dermat. & Syph. **26**:663 (Oct.) 1932. (*f*) Tappeiner, S.: Ueber das Vorkommen apokriner Drüsen in Naevusformationen, Arch. f. Dermat. u. Syph. **179**:144, 1939.

18. Pollitzer.[16b] Wolters.[16c] Frieboes.[16d] Ostrowski.[16e]

19. (*a*) Pautrier.[10] (*b*) Pollitzer.[16b] (*c*) Frieboes.[16d] (*d*) Ostrowski.[16e] (*e*) Robinson.[17e] (*f*) Masson, P., and Géry, L.: L'épithélioma sébacé, Bull. Assoc. franç. p. l'étude du cancer **11**:284, 1922. (*g*) Biberstein, H.: Talgdrüsennaevus und Epitheliom, Arch. f. Dermat. u. Syph. **147**:177, 1924. (*h*) Flarer, F.: Nota clinica ed istologica su un caso di adenoma sebaceo circoscritto, Arch. ital. di dermat., sif. **2**:282, 1926-1927. (*i*) Szodoray, L.: Relations Between Naevus Sebaceus and Epithelioma, Acta dermat.-venereol. **13**:1, 1932. (*j*) Loos, H. O.: Die Carcinome der Anhangsgebilde der Haut, Arch. f. Dermat. u. Syph. **174**:465, 1936. (*k*) Savatard, L.: Naevus Sebaceus and Sebaceous Carcinoma, Brit. J. Dermat. **53**:214, 1941.

20. (*a*) Woolhandler and Becker.[16f] (*b*) Carol, W. L. L.: Beitrag zur Kenntnis des Adenoma sebaceum (Pringle) und sein Verhältnis zur Krankheit von Bourneville und von Recklinghausen, Acta dermat.-venereol. **2**:186, 1921. (*c*) Butterworth, T., and Wilson, M., Jr.: Dermatologic Aspects of Tuberous Sclerosis, Arch. Dermat. & Syph. **43**:1 (Jan.) 1941. (*d*) Moolten, S. E.: Hamartial Nature of the Tuberous Sclerosis Complex and Its Bearing on the Tumor Problem, Arch. Int. Med. **69**:589 (April) 1942.

Since the sebaceous structures are not adenomatous but fully or almost fully developed and abnormal only by their presence in excessive numbers they regard the lesions as organic nevi rather than as adenomas. Bosellini,[21] Carol,[20b] Lang,[22] Butterworth and Wilson[20c] and Good and Garb[23] observed cases in which excessive development of

Fig. 2.—Nevus sebaceus (Jadassohn) of the scalp. Apocrine glands are present beneath the sebaceous glands.

21. Bosellini, P. L.: Ueber einen Fall des sogenannten Adenoma sebaceum Pringle (Symmetrischer Naevus des Gesichts), Monatsh. f. prakt. Dermat. **51**:495, 1910.

22. Lang, M.: Adenoma sebaceum, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1933, vol. 12, pt. 3, p. 487.

23. Good, C. K., and Garb, J.: Symmetric Nevi of Face, Tuberous Sclerosis, Epilepsy and Fibromatous Growth on Scalp, Arch. Dermat. & Syph. **47**:197 (Feb.) 1943.

sebaceous glands was absent. Instead, a large number of hair structures were noted, most of which were in an embryonal stage of development. Because of the frequent presence of hair structures, Carol [20b] suggested, in place of adenoma sebaceum, the name hamartoma pilosebaceum, a designation to which Butterworth and Wilson [20c] and Moolten [20d] have agreed.

Fig. 3.—Adenoma sebaceum (Pringle). Numerous embryonal hair structures, but only few sebaceous glands, are present in this case.

Several cases of adenoma sebaceum (Pringle) studied at the Massachusetts General Hospital contained embryonal hair structures in addition to sebaceous glands. In 1 case, the two excised nodules showed an exceedingly large number of embryonal hair structures and only a few sebaceous glands (fig. 3). In any event, since both sebaceous

glands and hair are primary epithelial germ structures, adenoma sebaceum is regarded as a primary epithelial germ tumor.

Apocrine Nevi.—Instances of organic nevi composed only of apocrine glands have not been found described in the literature. Apocrine glands may, however, be present in organic nevi together with other structures. It has been stated already that apocrine glands are frequently present in nevus sebaceus. A nevus verrucosus of the cheek observed at the Massachusetts General Hospital showed apocrine glands deep in the corium.

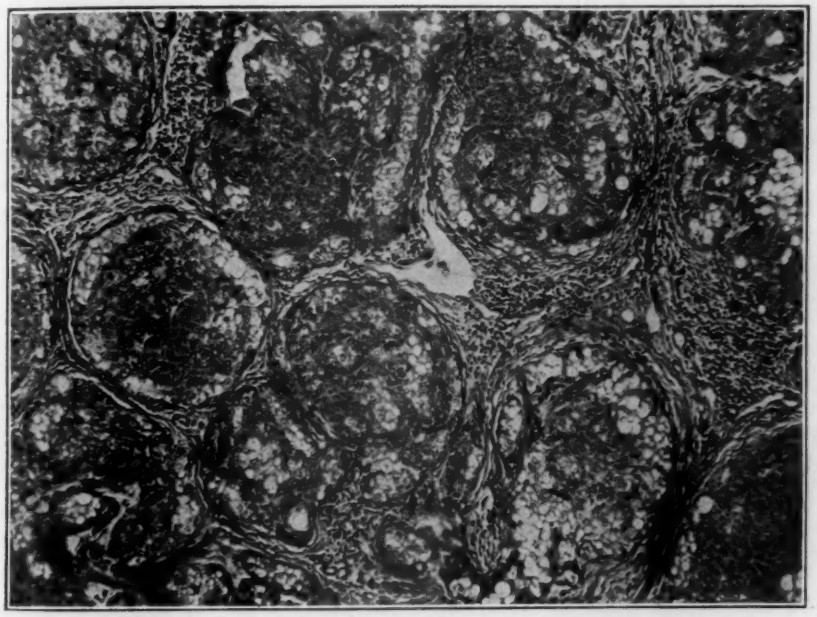

Fig. 4.—Sebaceous adenoma. The tumor is composed of lobules. Two types of cells can be discerned, generative and sebaceous cells.

Hair Nevi.—Purely hair nevi occur, but more commonly they appear in conjunction with other structures, i. e., with nevus sebaceus, papillomas or nevocellular nevi. Some cases of adenoma sebaceum (Pringle) are, as already stated, hair nevi rather than sebaceous nevi.

ORGANOID HAMARTOMAS (ADENOMAS)

The cutaneous adenomas show less differentiation than the nevi organomatosi. Nonetheless, well developed glandlike structures are present. The cells of the primary epithelial germ possess the potentiality to develop into either sebaceous adenomas or apocrine adenomas.

Sebaceous Adenoma.—Sebaceous adenoma, excessively rare, is a circumscribed, and in most instances encapsulated, tumor composed of

a large number of small lobules which resemble glandular acini (fig. 4). Two types of cells are present. The cells of the first type have large, elongated and strongly basophilic nuclei and only a small amount of cytoplasm, so that the nuclei lie close together. No sharp cell borders can be recognized. These cells thus closely resemble the cells of which basal cell epitheliomas are composed. They are identical with cells present at the neck and the periphery of normal sebaceous glands, the so-called generative cells ("cellules génératrices") of Grynfeltt.[24] These cells thus closely resemble the cells of which basal cell epitheliomas are composed. The cells of the second type are mature sebaceous cells. In addition, these are cells in a transitional stage of differentiation between these two types of cells ("cellules de transition" of Grynfeltt). Their presence is evidence that the sebaceous cells develop from the generative cells.

The distribution of the two types of cells within the lobules varies. Some lobules contain predominantly generative cells and, thus, resemble basal cell epithelioma. Other lobules contain mainly sebaceous cells and resemble mature sebaceous lobules. In most lobules, however, the two types of cells lie intermingled. As a rule, groups of sebaceous cells are surrounded by generative cells. Larger lobules may contain, in their center, cystic spaces formed by the decomposition of mature sebaceous cells. Sebaceous ducts surrounded by prickle cells may or may not be present in sebaceous adenoma. Staining with sudan III reveals the presence of fat in the sebaceous and transitional cells and in the cystic spaces.

The number of cases of sebaceous adenoma described in the literature is small.[25] Pautrier[10] and van der Valk[14] called the tumors which they reported sebaceous epitheliomas. The differentiation toward sebaceous structures is, however, so well marked that it appears justified to classify them as sebaceous adenomas.

Apocrine Adenomas.—Apocrine adenomas have large branching lumens bordered by cells which usually show active secretion. Two types occur, namely, syringocystadenoma papilliferum and hidradenoma papilliferum, the former with differentiation mainly toward duct cells and the latter with differentiation mainly toward gland cells.

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24. Grynfeltt, E.: Un cas d'épithélioma baso-sébacé. Etude des cellules génératrices des glandes sébacés. Leur importance dans la determination des tumeurs de ces glandes, Bull. Assoc. franç. p. l'étude du cancer **13**:474, 1924.

25. Pautrier.[10] van der Valk.[14] Woolhandler and Becker (cases 1 and 5).[16f] Bock, E.: Ueber ein Adenom der Talgdrüsen, Virchows Arch. f. path. Anat. **81**: 503, 1880. Reitmann, K.: Zur Kenntnis der Talgdrüsen und der von ihnen ausgehenden Wucherungs- und Neubildungsprozesse, Arch. f. Dermat. u. Syph. **99**: 125, 1909. Mallory, F. B.: The Principles of Pathologic Histology, Philadelphia, W. B. Saunders Company, 1925, p. 374. Warren, S., and Warvi, W. N.: Tumors of Sebaceous Glands, Am. J. Path. **19**:441, 1943.

Syringocystadenoma Papilliferum (Nevus Syringocystadenomatosus Papilliferus): While most authors regard this tumor as an adenoma of sweat glands in general, two recent writers have expressed the opinion that it is of apocrine origin.

Beck [26] expressed the belief that syringocystadenoma papilliferum was of apocrine origin because the glandular lumens occasionally lead into hair follicles and excess amounts of sebaceous glands are frequently present. Glasunow [27] noted that the glandular cells showed the same type of secretion as apocrine gland cells.

Vohwinkel [28] stated that the tubular structures greatly resembled apocrine glands. The fact, however, that in his case the ducts did not lead into hair follicles, but directly into the epidermis, was regarded by him as not in accordance with the apocrine theory. In answer to Vohwinkel's statement it may be said that, if it is assumed that syringocystadenoma papilliferum is a hamartoma of primary germ cells, these cells may form only apocrine glands without forming hair follicles and sebaceous glands too. Furthermore, several authors [29] have observed connections of the ducts of the tumor with hair follicles.

Tappeiner [17f] noted apocrine glands in sections of a syringocystadenoma papilliferum, but he did not imply that this tumor was of apocrine origin.

My own observations on 6 cases support the theory that syringocystadenoma papilliferum is an apocrine adenoma.

First, the lumens of the tumor are lined by two rows of epithelial cells, with the cells of the inner row frequently showing active secretion of the type seen in apocrine glands. Several authors [30] have previously observed evidence of active secretion in the cells lining the lumens. Second, apocrine glands are frequently present beneath

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26. Beck, S. C.: Syringoma, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1933, vol. 12, pt. 3, p. 458,

27. Glasunow, M.: Ueber die gutartigen Geschwülste der Schweissdrüsen, Ztschr. f. Krebsforsch. **33**:431, 1931.

28. Vohwinkel, K. H.: Ueber das Vorkommen apokriner Drüsen, Dermat. Ztschr. **60**:314, 1931.

29. (*a*) Kreibich, K.: Ein Fall von "Adenoma folliculare cutis papilliferum," Arch. f. Dermat. u. Syph. **70**:3, 1904. (*b*) Hedinger, E.: Zur Frage des Plasmocytoms, Frankfort. Ztschr. f. Path. **7**:343, 1911. (*c*) Arzt, L., and Kumer, L.: Ueber Drüsennävi, Arch. f. Dermat. u. Syph. **148**:323, 1925. (*d*) Biberstein, H.: Ueber papilliforme Syringocystadenome, ibid. **152**:602, 1926. (*e*) Dörffel, J.: Zur Histogenese des Naevus syringocystadenomatosus papilliferus, Dermat. Wchnschr. **101**:854, 1935.

30. (*a*) Glasunow.[27] (*b*) Klauber, O.: Ueber Schweissdrüsentumoren, Beitr. z. klin. Chir. **41**:311, 1904. (*c*) Hoffmann, E., and Frieboes, W.: Zur Kenntnis der Schweissdrüsennaevi mit besonderer Berücksichtigung des Naevus syringadenomatodes papilliferus und Bemerkungen über epitheliale Naevi, Dermat. Ztschr. **27**:255, 1919.

the tumor (fig. 5). Connections of these glands with the lumens of the tumor can be traced without difficulty. Large glandular lumens beneath syringocystadenoma papilliferum have been observed by previous writers. Most of them [31] referred to them as dilated sweat glands. Tappeiner [17f]

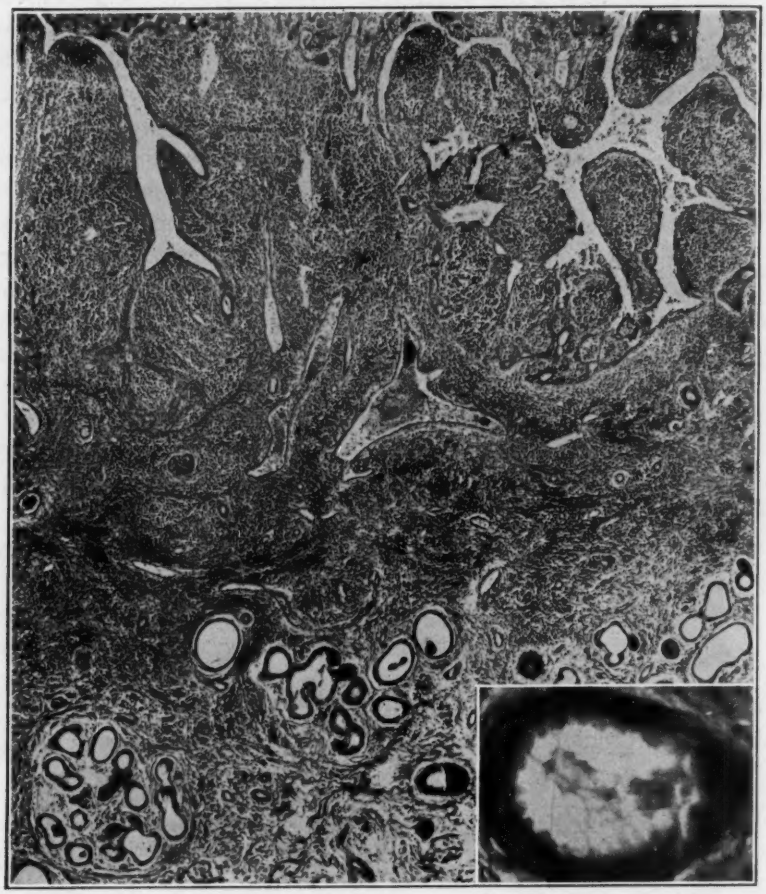

Fig. 5.—Syringocystadenoma papilliferum. Apocrine glands are present deep in the corium. The inset shows one of the aprocrine glands in high magnification. The lumen is lined by actively secreting cells.

31. (*a*) Dörffel.[29e] (*b*) Rothe, L.: Ueber einen Fall von Naevus syringocystadenomatosus (Hidrocystoma papilliferum) mit Plasmom, Arch. f. Dermat. u. Syph. **113**:887, 1912. (*c*) Werther, J.: Syringadenoma papilliferum (Naevus syringadenomatosus papilliferus), ibid. **116**:865, 1913. (*d*) Cardenal, C.: Zur Kenntnis der Histologie des Syringocystadenoma papilliferum, ibid. **166**:315, 1932. (*e*) Fessler, A.: Ein Fall von Naevus syringocystadenomatosus papilliferus, Dermat. Wchnschr. **96**:680, 1933. (*f*) Sachs, W., and Lewis, G. M.: Naevus Syringadenomatosus Papilliferus, Arch. Dermat. & Syph. **36**:1202 (Dec.) 1937. (*g*) Nödl, F.: Beitrag zum Naevus syringo-cystadenomatosus papilliferus, Arch. f. Dermat. u. Syph. **178**:697, 1939. (*h*) Wolters, M.: Naevi syringoadenomatosi, ibid. **70**:375, 1904.

regarded them as apocrine glands. Third, connections of the lumens of the tumor as well as of the large tubular glands beneath the tumor

Fig. 6.—Syringocystadenoma papilliferum. A large apocrine gland is shown in direct connection with a hair follicle.

with hair follicles were noted in one instance (fig. 6). Such connections with hair follicles have been observed by several authors.[29] Fourth,

in 4 of the 6 cases excess amounts of mature or nearly mature sebaceous glands were observed within the tumor, so that the impression was gained that these cases represented a combination of syringocystadenoma papilliferum and nevus sebaceus. This combination suggests a common origin for both, namely, the primary epithelial germ. Several authors previously reported the association of syringocystadenoma papilliferum with nevus sebaceus [32] or with basal cell epithelioma.[33]

Hidradenoma Papilliferum: Hidradenoma papilliferum, which occurs almost exclusively on the labia majora, has lumens lined by actively secreting cells and shows papillary projections into its lumens. Sometimes, myoepithelial cells appear peripheral to the secretory cells, either arranged in a single layer or proliferating irregularly into the interstitial tissue.

Krompecher [34] and Gates, Warren and Warvi [35] pointed out that the papillary hidradenomas closely resemble the papillary cystadenomas of the mammary gland. It should be remembered that, phylogenetically, the mammary gland is an apocrine gland. Danforth [36] expressed the opinion that the hidradenomas of the vulva were apocrine gland tumors. McDonald [37] recently published a study of 30 cases of "apocrine sweat gland carcinoma of the vulva." None of them showed a recurrence after excision, and no metastases were observed. In spite of this, he regarded them as adenocarcinomas, "because of their histologic character and infiltrative nature." A study of his photomicrographs suggests that the cells referred to as infiltrative carcinomatous cells are myoepithelial cells and that the tumors are papillary hidradenomas.

SUBORGANOID HAMARTOMAS (BENIGN EPITHELIOMAS)

The benign epitheliomas originate from primary epithelial germ cells which, prior to the onset of neoplasia, attained less differentiation than those from which the adenomas originate, yet sufficient differentiation to form structures which show distinct resemblance to the cutaneous appendages. In short, there is a further step-down from the organoid tumors in respect to differentiation.

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32. Arzt and Kumer.[29c] Dörffel.[29e]

33. Kreibich.[29a] Hedinger.[29b] Dörffel.[29e] Nödl.[31g] Reuterwall, O.: Naevus Syringo-Cystadenomatosus papilliferus and Its Relation to Malignancy, Acta path. et microbiol. Scandinav., 1933, supp. 16, p. 376.

34. Krompecher, E.: Zur Kenntnis der Geschwülste und Hypertrophien der Schweissdrüsen, Arch. f. Dermat. u. Syph. **126**:765, 1918-1919.

35. Gates, O.; Warren, S., and Warvi, W. N.: Tumors of Sweat Glands, Am. J. Path. **19**:591, 1943.

36. Danforth, W. C.: Hydradenoma Vulvae, Am. J. Obst. & Gynec. **45**:329, 1943.

37. McDonald, J. R.: Apocrine Sweat Gland Carcinoma of the Vulva, Am. J. Clin. Path. **11**:890, 1941.

Jadassohn,[11] who regarded epithelioma adenoides cysticum, syringoma and cylindroma as benign epitheliomas, stated the belief that they arose from displayed embryonal cells and, therefore, were nevi. Many writers have concurred with this view. Kyrle [38] stated the belief that the benign epitheliomas originated from embryonal cells which had already progressed to a certain differentiation. Fischer [8] expressed the opinion that syringoma and epithelioma adenoides cysticum originated from the primary epithelial germ, because differentiation in these tumors usually is directed toward more than one of the three primary epithelial germ structures.

There are three groups of benign epitheliomas: sebaceous epitheliomas, apocrine epitheliomas and trichoepitheliomas.

Sebaceous Epithelioma (Epithélioma baso-sébacé of Grynfeltt, carcinoma sebaceum basocellulare of Loos).—In degree of differentiation, sebaceous epithelioma stands between sebaceous adenoma with its more typical lobules, on the one hand, and cystic basal cell epithelioma in which there is only little differentiation toward sebaceous cells, on the other. As Loos [19j] put it, it grows like a basal cell epithelioma, but its cells have undergone considerable differentiation toward sebaceous cells.

Unlike sebaceous adenomas, sebaceous epitheliomas are not sharply circumscribed, they do not show lobular arrangement and fewer cells are typically sebaceous. They are composed of irregularly shaped epithelial masses and branching strands which infiltrate into the corium. The architecture thus resembles that of basal cell epithelioma (fig. 7), The majority of cells are generative and transitional cells.[24] There are only small groups of mature sebaceous cells, which usually are located in the centers of the masses and strands. Cysts formed by the disintegration of cells may or may not be present.

Sebaceous epithelioma is an uncommon type of tumor. Ménétrier and Durant [39] appear to have been the first authors to have described it. Further examples have been reported by Ménétrier and Isch-Wall,[40] Masson and Géry (case 3),[19f] Grynfeltt,[24] Biberstein,[19g] and Milian, Périn and Brunel.[41] In Biberstein's case the sebaceous epithelioma arose within a nevus sebaceus. In Grynfeltt's case a basal cell epithelioma was present close to the sebaceous epithelioma.

38. Kyrle, J.: Vorlesungen über Histo-Biologie der menschlichen Haut und ihrer Erkrankungen, Berlin, Julius Springer, 1925, vol. 1, p. 287.

39. Ménétrier, P., and Durand, A.: Epithélioma sébacé, Bull. et mém. Soc. anat. de Paris **90**:441, 1920.

40. Ménétrier, P., and Isch-Wall, P.: Epithélioma sébacé, Bull. Assoc. franç. p. l'étude du cancer **11**:144, 1922.

41. Milian; Périn, L., and Brunel: Epithélioma sébacé, Bull. Soc. franç. de dermat. et syph. **40**:553, 1933.

Apocrine Epitheliomas.—Unlike the apocrine adenomas, which have large branching lumens, apocrine epitheliomas have small lumens or no lumens at all. Three types of apocrine epitheliomas occur: syringoma, cylindroma and myoepithelioma. It is my belief that all syringomas and cylindromas and most myoepitheliomas represent tumors of primary

Fig. 7.—Sebaceous epithelioma. This tumor has an architecture similar to that of basal cell epithelioma, but many of its cells show a considerable degree of differentiation toward sebaceous cells.

epithelial germ cells, although some myoepitheliomas may originate from eccrine gland germ cells. While in syringoma differentiation is directed mainly toward duct cells, differentiation in cylindroma is directed mainly toward gland cells and in myoepithelioma mainly toward myoepithelial cells.

Syringoma: The relationship of the cells in syringoma to sweat gland cells has long been recognized and has been the reason for general acceptance of the name syringoma, which was first suggested by Unna.[42] In recent years several authors have expressed their belief that syringomas have an apocrine origin.

Kyrle,[43] in 1924, concluded that syringomas developed from aberrant apocrine glands, because he found fragments of cells within the lumens indicative of apocrine secretion. He also pointed out that the lesions usually develop at puberty, which is the time when apocrine glands begin to function. Fischer [8] stated the belief that syringomas developed from primary epithelial germ cells which differentiate toward apocrine cells. His reason for regarding the primary epithelial germ as the origin of syringoma was the presence of a rudimentary hair follicle in a section of syringoma which he had examined. Beck [44] expressed himself in favor of apocrine origin, because he observed connections between the syringoma and hair follicles. Weidman and Besancon [45] observed that "large numbers of finer and coarser red globules more or less crowded the cytoplasm of the glandular cells and recalled the granules seen in the apocrine members of the axillary glands." Riehl,[46] too, saw necrobiotic apocrine secretion. Additional authors who regard syringoma as an apocrine tumor are Wendlberger,[47] Rosenberg [48] and Homma and Escher.[49]

Montgomery,[2f] however, stated that in a study of 7 cases he found no proof that syringoma was an apocrine gland tumor, since in no case could mature apocrine glands be detected within or in the vicinity of the tumors. Vohwinkel [28] argued against the apocrine origin of syringoma, because the epithelial ducts and strands did not show connections with hair follicles.

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42. Unna, P. G.: Die Histopathologie der Hautkrankheiten, Berlin, A. Hirschwald, 1894, p. 1138.

43. Kyrle, J.: Vorlesungen über Histo-Biologie der menschlichen Haut und ihrer Erkrankungen, Berlin, Julius Springer, 1925, vol. 1, p. 245.

44. Beck, S. C.: Epitheliome, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1933, vol. 12, pt. 3, p. 458.

45. Weidman, F. D., and Besancon, J. H.: Histologic Differences in a "Syringoma" of the Face and Shoulder, Arch. Dermat. & Syph. **21**:279 (Feb.) 1930.

46. Riehl, G., Jr.: Zur Histogenese des Syringocystadenoms, Wien. klin. Wchnschr. **48**:209, 1930.

47. Wendlberger, J.: Beitrag zur Histogenese der Syringome, Arch. f. Dermat. u. Syph. **176**:467, 1938.

48. Rosenberg, W. A.: Syringoma Influenced by X-Ray Therapy, Urol. & Cutan. Rev. **37**:295, 1933.

49. Homma, H., and Escher, D. H. E.: Genesis of Syringoma, Arch. Dermat. & Syph. **33**:700 (April) 1936.

Fig. 8.—Syringoma (below) and trichoepithelioma (above) in the same lesion.

Fischer's view of the origin of syringoma from primary epithelial germ cells would invalidate Montgomery's and Vohwinkel's arguments. Presence of mature apocrine glands and connections with hair follicles are not a prerequisite, if it is assumed that syringoma, as a hamartoma, originates not from mature apocrine glands or hair follicles but from embryonal cells.

I regard, in agreement with the aforementioned authors,[50] syringoma as an apocrine tumor, because also in the cases studied at the Massachusetts General Hospital the tubular structures were occasionally lined by cells which appeared to be actively secreting or disintegrating in the process of secretion. The absence of active secretion in most lumens can be explained by insufficient differentiation and by the fact that the direction of differentiation is toward apocrine duct cells rather than gland cells. A further argument in favor of an apocrine origin is the simultaneous occurrence of syringoma and epithelioma adenoides cysticum in the same patient[51] and even in the same lesion (fig. 8). This suggests a common genesis for both, namely, the primary epithelial germ.

Cylindroma: While in syringoma the close relation to sweat gland formations is generally accepted, the pathogenesis of cylindroma is less clearly established. Some authors have expressed the belief that cylindroma originates from sweat glands and others that it originates from hair follicles.

Frieboes,[52] Coenen,[53] Davies,[54] Weidman,[55] Ricker and Schwalb[56] and Jones, Alden and Bishop[57] regarded cylindroma as a sweat gland

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50. Kyrle.[43] Beck.[44] Weidman and Besancon.[45] Riehl.[46] Wendlberger.[47] Rosenberg.[48] Homma and Escher.[49]

51. (*a*) Weidman and Besancon.[45] (*b*) Wolters, M.: Epithelioma adenoides cysticum, Arch. f. Dermat. u. Syph. **56**:89 and 197, 1901. (*c*) Perthes, G.: Ueber gutartige Epitheliome, wahrscheinlich congenitalen Ursprungs, Deutsche Ztschr. f. Chir. **65**:283, 1902. (*d*) Hartzell, M. B.: Benign Cystic Epithelioma, and Its Relationship to So-Called Syringocystadenoma, Syringocystoma and Haemangio-Endothelioma, Brit. J. Dermat. **16**:361, 1904. (*e*) Schopper, K. J.: Epithelioma adenoides cysticum (Brooke), Arch. f. Dermat. u. Syph. **98**:199, 1909. (*f*) McDonagh, J. E. R.: Mixed Tumor (Trichoepithelioma Papulosum and Syringo-Cystadenoma), Brit. J. Dermat. **22**:20, 1910. (*g*) Ingels, A. E.: Epithelioma Adenoides Cysticum with Features of Syringoma, Arch. Dermat. & Syph. **32**:75 (July) 1935. (*h*) Montgomery, H., and Kierland, R. R.: Metastasis of Carcinoma to the Scalp, Arch. Surg. **40**:672 (April) 1940.

52. Frieboes, W.: Beitrag zur Klinik und Histopathologie der gutartigen Hautepitheliome, Berlin, S. Karger, 1912.

53. Coenen, H.: Das Hidradenoma cylindromatosum der Kopfschwarte, Beitr. z. klin. Chir. **95**:205, 1915.

54. Davies, J. H. T.: A Contribution to the Histology of the Cylindromatous Tumors of the Scalp, Brit. J. Dermat. **40**:241, 1923.

(Footnotes continued on next page)

tumor. Hoffmann,[30c] Pinkus,[58] Watanabe,[59] Burnier and Rejsek,[60] Voigt,[61] Wiedemann,[62] Stillians [63] and Schlammadinger [64] interpreted cylindroma as a hair follicle tumor. Watanabe [59] considered the possibility that it might develop from misformed sweat glands belonging to the hair.

The theory of the apocrine origin of cylindroma would reconcile both schools of thought, since it would account for the presence of glandular structures as well as their connections with hair follicles. The view that cylindroma is an apocrine tumor has already been expressed by Balog [17c] and Schuermann and Weber.[65]

Microscopic examination of my 7 cases of cylindroma presented the following evidence for the apocrine origin of cylindroma.

First, in 1 case there were obvious apocrine gland lumens (fig. 9). Two rows of epithelial cells surrounded the lumens, an inner row of actively secreting cells and an outer row of myoepithelial cells.

Second, two types of epithelial cells could be discerned in all 7 cases of cylindroma. Cells with large oval, light-staining nuclei were seen in the center of epithelial masses. They were regarded as cells differentiating toward secretory cells of apocrine glands. Cells with small round or elongated dark-staining nuclei were observed arranged in palisade formation at the periphery of the epithelial masses and also scattered between the cells of the first type. They were regarded as cells differentiating toward myoepithelial cells of apocrine glands. The number of secretory cells was larger than that of the myoepithelial cells in every case. The presence of two types of cells in cylindroma has been noted by

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55. Weidman, F. D., in discussion on Stillians.[63]

56. Ricker, G., and Schwalb, J.: Die Geschwülste der Hautdrüsen, Berlin, S. Karger, 1914.

57. Jones, J. W.; Alden, H. S., and Bishop, E. L.: Turban Tumor, or Sweat Gland Carcinoma, Arch. Dermat. & Syph. **26**:656 (Oct.) 1932.

58. Pinkus, F.: Fall von Zylindromen (Spiegelerschen Tumoren) der Kopfhaut und des Rumpfes, Dermat. Ztschr. **34**:218, 1921.

59. Watanabe, J.: Ueber das Cylindrom und das Epithelioma adenoides cysticum, Arch. f. Dermat. u. Syph. **140**:208, 1922.

60. Burnier and Rejsek: Tumeurs multiples du cuir chevelu, Bull. Soc. franç. de dermat. et syph. **30**:90, 1923.

61. Voigt: Zylindroma, Dermat. Wchnschr. **82**:581, 1926.

62. Wiedemann, A.: Weitere Beiträge zur Kenntnis der sogenannten Zylindrome der Kopfhaut (Spiegler), Arch. f. Dermat. u. Syph. **159**:180, 1930.

63. Stillians, A. W.: Naevo-Epithelioma Adenoides (Cylindroma) of the Scalp, Arch. Dermat. & Syph. **27**:481 (March) 1933.

64. Schlammadinger, J.: Cylindrom und Trichoepithelioma papulosum multiplex, Arch. f. Dermat. u. Syph. **171**:526, 1935.

65. Schuermann, H., and Weber, K.: Beitrag zur Kenntnis der Spiegler'schen Tumoren (Cylindrome) nebst einigen Bemerkungen zum Epithelioma adenoides cysticum, Arch. f. Dermat. u. Syph. **175**:682, 1937.

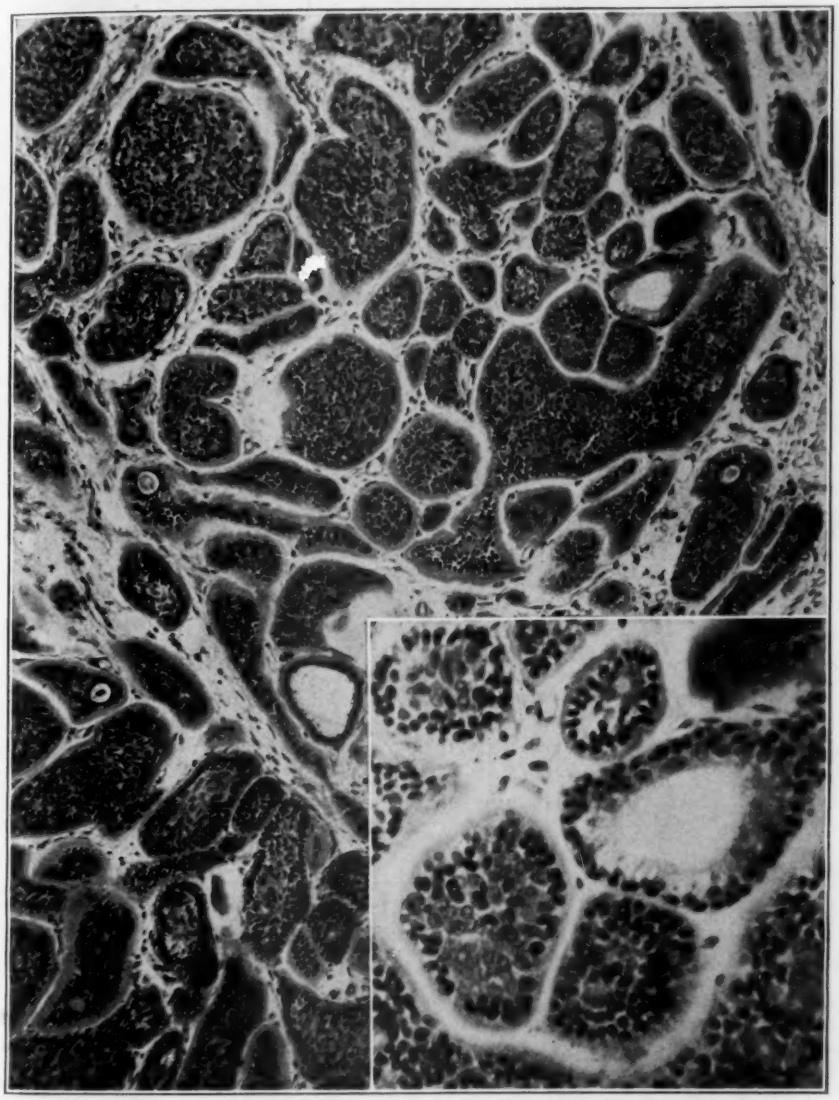

Fig. 9.—Cylindroma. Two types of cells can be discerned: one type has large oval pale nuclei and the other small round or elongated dark-staining nuclei. In the right upper corner is a glandular lumen showing evidence of active secretion. The inset shows the glandular lumen in high magnification.

many observers,[66] but none of them has tried to explain the nature of the two types of cells.

Third, the simultaneous presence of cylindroma and epithelioma adenoides cysticum in the same patient was observed in one instance. This occurrence has been repeatedly reported.[67] Watanabe [59] has even observed both types of tumors in the same lesion. The assumption that both tumors develop from the primary epithelial germ appears to be the most satisfactory explanation for their simultaneous presence.

Myoepithelioma (Myoepithelial Sweat Gland Tumor): Myoepitheliomas are sharply circumscribed usually encapsulated essentially solid tumors. The cells are arranged either in intertwining bands or in lobular masses. The same two types of cells are present as in cylindroma, but, in contrast to cylindroma, the majority of cells are myoepithelial cells. The secretory cells lie in small groups and frequently are arranged around small lumens. The myoepithelial cells are located, in the epithelial bands, at the periphery end, in the lobules, around and between the groups of secretory cells (fig. 10). Some of the tumors possess a considerable amount of stroma of hyaline appearance and thus resemble the so-called mixed tumors of salivary glands.

Darier [68] first mentioned the presence of myoepithelial cells in sweat gland tumors. Grynfeltt and Aimes [69] described the first myoepithelioma, calling it "adéno-épithéliome sudorifère." Additional cases have been described by Sutton,[70] Balog [71] and Sheldon (case 1).[72]

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66. (*a*) Balog.[17c] (*b*) Glasunow.[27] (*c*) Frieboes.[52] (*d*) Watanabe.[59] (*e*) Weidemann.[62] (*f*) Stillians.[63] (*g*) Schlammadinger.[64] (*h*) Biberstein, H.: Epithelioma adenoides cysticum im Gesicht und Cylindrome am behaarten Kopf, Arch. f. Dermat. u. Syph. **142**:428, 1923. (*i*) Kogoj, F.: Ueber das Verhalten des Hyalins in Cylindromen, ibid. **166**:515, 1932. (*j*) Zakon, S. J.: Naevo-Epithelioma Adenoides (Cylindroma) of the Scalp, Arch. Dermat. & Syph. **40**: 945 (Dec.) 1939.

67. (*a*) Frieboes.[52] (*b*) Watanabe.[59] (*c*) Burnier and Rejsek.[60] (*d*) Schlammadinger.[64] (*e*) Schuermann and Weber.[65] (*f*) Biberstein.[66h] (*g*) Adamson, H. G.: Epithelioma Adenoides Cysticum of Brooke in Mother, Daughter and Two Sons, Associated with So-Called "Multiple Endotheliomas of the Scalp": Its Relationship to Multiple Rodent Ulcer, Proc. Roy. Soc. Med. **7**:95, 1913-1914. (*h*) Savatard, L.: Epithelioma Adenoides Cysticum, Brit. J. Dermat. **50**:333, 1938.

68. Darier, J.: Contribution à l'étude de l'épithéliome des glandes sudoripares, Arch. de méd. expér. et d'anat. path. **1**:115 and 267, 1889.

69. Grynfeltt, E., and Aimes, A.: Etude histo-pathologique des deux tumeurs des glandes sudoripares, Bull. Assoc. franç. p. l'étude du cancer **11**:91, 1922.

70. Sutton, R. L. Jr.: A Rare Sweat Gland Tumor, Arch Dermat. & Syph. **30**:195 (Aug.) 1934.

71. Balog, P.: Beitrag zur Frage der Schweissdrüsenadenome, Adenoma hydradenoides parenchymatosa cum lymphostasi, Acta dermat.-venereol. **22**:187, 1941.

72. Sheldon, W. H.: The Myoepithelium in Sweat Gland Tumors, Arch. Path. **31**:326 (March) 1941.

Regarding the pathogenesis of myoepithelioma, Sutton's case and the 3 cases studied at the Massachusetts General Hospital are believed to be of apocrine origin, because of the presence of active secretion. In the cases reported by Grynfeltt and Aimes [69] and Balog [71] the eosinophilic staining of the glandular cells suggests also an apocrine genesis, but

Fig. 10.—Myoepithelioma (myoepithelial sweat gland tumor). Two types of cells can be seen: Secretory cells are arranged around lumens; they show evidence of active secretion; myoepithelial cells fill the spaces between the lumens and are in the majority.

insufficient differentiation of the glandular structures makes it impossible to rule out an eccrine origin. Unlike the other benign epitheliomas, myoepithelioma has never been observed associated with other tumors the origin of which would permit one to draw conclusions as to its

origin. It is possible that some myoepitheliomas are of apocrine and others of eccrine origin.

Trichoepithelioma (Epithelioma Adenoides Cysticum, Multiple Benign Epithelioma).—The name trichoepithelioma, first suggested by Jarisch,[73] seems preferable to the others, because differentiation is directed mainly toward hair structures.

The occasional presence of connections between trichoepithelioma and mature hair follicles has led many authors to the conclusion that trichoepithelioma originates from mature hair follicles.[74] Paul and Adamson [75] regarded embryonal pilosebaceous follicles and Schlammadinger [64] embryonal hair germs as the site of origin of trichoepithelioma. Fischer [8] expressed the belief that trichoepithelioma was a tumor originating from primary epithelial germs. He pointed out that, occasionally, differentiation took place not only to hair but also to other primary epithelial germ structures, such as apocrine glands.

It is my belief, with Fischer, that trichoepithelioma is a tumor of primary epithelial germ cells. Although differentiation is directed mainly toward hair structures, occasionally apocrine glands [76] and sebaceous glands [51g] are present. Furthermore, the repeatedly reported association of trichoepithelioma with other benign epitheliomas, such as syringoma [77] and cylindroma,[78] in the same patient suggests a common origin for these tumors, namely, the primary epithelial germ.

"Horn cysts" are the characteristic lesion in trichoepithelioma. In addition, abortive hair papillae and hair shafts are often seen (fig. 11). The "horn cysts" consist of a fully keratinized center surrounded, as a rule, by cells without prickles. Only occasionally prickle cells are seen. The horn cells of the "cysts" seem to develop from cells without prickles. This process corresponds to the development of the horn cells of the hair from hair matrix cells, which are also cells without prickles. It is concluded that the cells surrounding the "horn cysts" are hair matrix cells and that the "horn cysts" represent attempts at hair shaft formation.

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73. Jarisch, A.: Zur Lehre von den Hautgeschwülsten, Arch. f. Dermat. u. Syph. **28**:163, 1894.

74. Hartzell.[51d] Frieboes.[52] Ricker and Schwalb.[56] Jarisch.[73] Shoemaker, J. V., and Boston, L. N.: Benign Cystic Epithelioma, J. A. M. A. **47**:1147 (Oct. 13) 1906. Werther, J.: Trichoepithelioma (Naevus tricho-epithelioma-tosus), Arch. f. Dermat. u. Syph. **88**:334, 1907.

75. Paul, S. N., and Adamson, H. G.: A Case of Syringoma, Brit. J. Dermat. **28**:106, 1916.

76. Fischer.[8] Hval, E.: Adenomata of Sweat Glands and Other Kindred Tumours: Their Generic Relationship to Naevi, Acta dermat.-venereol. **17**:1, 1936.

77. Weidman and Besancon.[45] Footnotes 51 *b, c, d, e, f, g* and *h*.

78. Frieboes.[52] Watanabe.[59] Burnier and Rejsek.[60] Schlammadinger.[64] Schuermann and Weber.[65] Biberstein.[66h] Adamson.[67g] Savatard.[67h]

The prickle cells which occasionally are seen around the cysts probably represent outer hair sheath cells, which are cells possessing prickles. Since the outer hair sheath develops from prickle cells at a time when the primary epithelial germ has already advanced to a rather high state of differentiation, the presence of prickle cells in a trichoepithelioma is regarded as evidence of rather high differentiation.

Tumors in an intermediate stage between trichoepithelioma and basal cell epithelioma occur clinically as well as histologically, so that it is impossible to draw a sharp line of demarcation between the two.

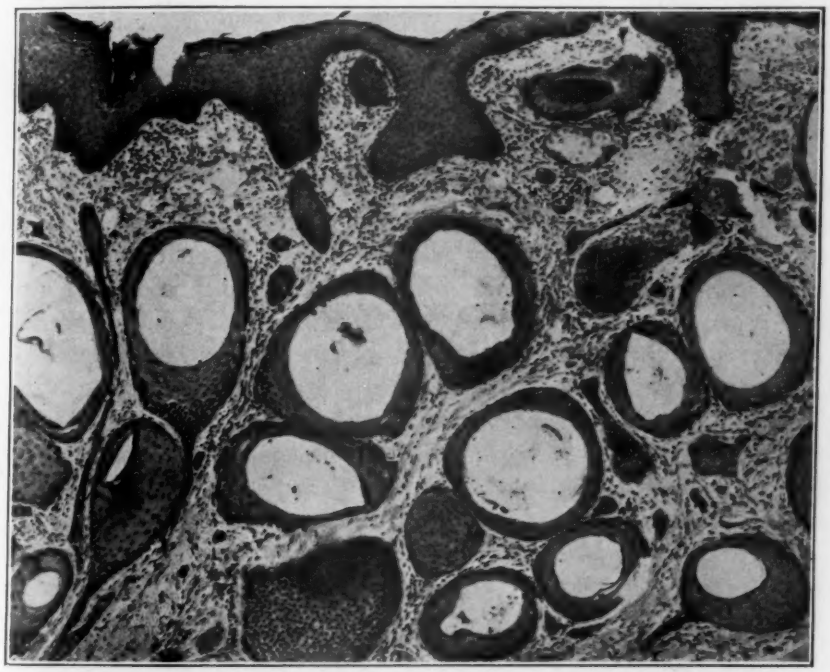

Fig. 11.—Trichoepithelioma (epithelioma adenoides cysticum). In the center, near the epidermis, two rudimentary hairs can be seen.

This is well illustrated by the disparity between the "conservative" definition of trichoepithelioma by Summerill and Hutton and the "liberal" definition by Traenkle and Weidman. Summerill and Hutton [79] limited the term epithelioma adenoides cysticum to cases in which multiple lesions developed before puberty and in which none of the lesions showed ulceration. All cases with ulceration of one or more lesions were regarded as instances of multiple basal cell epithelioma. Their definition

79. Summerill, F., and Hutton, J. G.: Multiple Benign Cystic Epithelioma (Epithelioma Adenoides Cysticum), Arch. Dermat. & Syph. **26**:854 (Nov.) 1932.

was, thus, based on clinical characteristics. On the other hand, Traenkle [80] and Weidman,[81] basing their definition on histologic grounds, included under trichoepithelioma many solitary lesions with the clinical appearance of basal cell epitheliomas, because histologically they showed evidence of keratinization.

Adamson [82] admitted the impossibility of a sharp differentiation between epithelioma adenoides cysticum and basal cell epithelioma. He saw the reason for this in their common origin. He stated the belief that both were "naevoid growths" and represented abortive attempts to form pilosebaceous follicles. The only difference, in his opinion, was that in basal cell epithelioma the cells were more embryonal than in epithelioma adenoides cysticum. Adamson's view was shared by McDonagh.[83]

It is my belief, with Adamson, that basal cell epithelioma and trichoepithelioma differ only in the degree of maturity of their cells. Since cells of various maturity may occur in the same lesion it is not uncommon to encounter in basal cell epithelioma areas consistent with the histologic picture of trichoepithelioma and vice versa. On a histologic basis, a differentiation of basal cell epithelioma and trichoepithelioma may, therefore, be impossible, and in order to arrive at a diagnosis in a given case it may be necessary to have knowledge of clinical data, such as the number and distribution of the lesions and the age at which the lesions first appeared. Though it may seem arbitrary, I prefer, in contrast to Traenkle [80] and Weidman,[81] to limit the diagnosis of trichoepithelioma to cases in which there are multiple lesions and suggest that solitary lesions, even if they show a degree of differentiation approaching that of trichoepithelioma, are classified not as trichoepithelioma but as keratotic basal cell epithelioma. On the other hand, I do not believe, as Summerill and Hutton [79] do, that in a case with multiple lesions the presence of

80. Traenkle, H. L.: Epithelioma Adenoides Cysticum, Trichoepithelioma and Basal Cell Cancer, Arch. Dermat. & Syph. **42**:822 (Nov.) 1940.

81. Weidman, F. D., in discussion on Traenkle.[80]

82. Adamson, H. G.: Two Cases of Multiple Rodent Ulcer, with a Note on the Possible Relationship Between Multiple Rodent Ulcer and Epithelioma Adenoides Cysticum of Brooke, Lancet **2**:1133, 1908; On the Nature of Rodent Ulcer: Its Relationship to Epithelioma Adenoides Cysticum of Brooke and to Other Tricho-Epitheliomata of Benign, Nevoid Character; Its Distinction from Malignant Carcinoma, ibid. **1**:810, 1914; in discussion on Little, E. G. G.: A Case for Diagnosis:? Multiple Rodent Ulcer or Epithelioma Adenoides Cysticum, Brit. J. Dermat. **27**:20, 1915; Case of Multiple Superficial Rodent Ulcer: Possible Embryonic Sweat-Duct Origin, Proc. Roy. Soc. Med. **16**:24, 1922-1923. Footnote 67 *g*.

83. McDonagh, J. E. R.: A Classification and Description of the Cutaneous Epitheliomata, J. Cutan. Dis. **32**:11, 1914.

ulceration in one or several lesions excludes a diagnosis of trichoepithelioma. If active growth occurs in a lesion of trichoepithelioma, the newly formed cells may be more embryonal than the older cells and the lesion may grow as basal cell epithelioma and ulcerate. Cases in which one or several of the lesions of trichoepithelioma, after having persisted as such for many years, developed into ulcers with the histologic picture of basal cell epithelioma have been reported by several authors.[84]

SUMMARY

Several groups of cutaneous tumors originate from the primary epithelial germ.

Primary epithelial germs begin to appear in the embryonal stratum germinativum during the third and fourth month of embryonal life. They differentiate into sebaceous glands, apocrine glands and hair. Tumors arising from primary epithelial germ cells, therefore, show various degrees of differentiation toward sebaceous glands, apocrine glands and hair.

Since the primary epithelial germ is an embryonal structure, tumors arising from it are nevoid tumors (hamartomas).

The type of tumor depends on the degree and direction of differentiation in the primary epithelial germ cells prior to the onset of neoplasia. More highly differentiated primary epithelial germ cells give rise to more highly differentiated tumors.

The primary epithelial germ tumors may be divided, according to the decreasing degree of organization and differentiation, into four groups: organic hamartomas (nevi organomatosi), organoid hamartomas (adenomas), suborganoid hamartomas (benign epitheliomas) and nonorganic hamartomas (basal cell epitheliomas). Each of the four groups may be subdivided, according to the direction of differentiation, into hamartomas with differentiation toward sebaceous gland, apocrine gland and hair structures.

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84. Frieboes.[52] Savatard.[67h] Jarisch.[78] White, J. C.: Multiple Benign Cystic Epithelioma, J. Cutan. & Genito-Urin. Dis. **12**:477, 1894. Schamberg, J. F.: A Case of Multiple Benign Cystic Epitheliomata, J. Cutan. Dis. **27**:170, 1909. Stelwagon, H. W.: A Treatise on Diseases of the Skin, ed. 8, Philadelphia, W. B. Saunders Company, 1916, p. 682. Sutton, R. L., and Dennie, C. C.: Possible Interrelationship of Acanthoma Adenoides Cysticum (Multiple Benign Cystic Epithelioma) and Syringocystadenoma (Lymphangioma Tuberosum Multiplex), J. A. M. A. **58**:333 (Feb. 3) 1912. Dore, S. E., in discussion on Little, E. G. G.: A Case for Diagnosis: (?) Multiple Rodent Ulcer or Epithelioma Adenoides Cysticum, Brit. J. Dermat. **27**:20, 1915. Little, E. G. G.: Epithelioma Adenoides Cysticum of Brooke, with Rodent Ulceration, ibid. **31**:193, 1919.

Although in all tumors the differentiation is directed mainly toward one primary epithelial germ structure, many show, in addition, differentiation toward the other two primary epithelial germ structures. The occurrence of transitional forms between the various tumors and of combinations of two or more varieties of primary epithelial germ tumors in the same patient and even in the same lesion is evidence of the close relationship between the tumors arising from the primary epithelial germ.

PATHOGENESIS OF BENIGN TUMORS OF CUTANEOUS APPENDAGES AND OF BASAL CELL EPITHELIOMA

II. Basal Cell Epithelioma

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IT IS THE thesis of this paper that the basal cell epitheliomas originate from incompletely differentiated embryonal cells rather than from dedifferentiated anaplastic cells. It is my belief that basal cell epitheliomas are not carcinomas, not derived from basal cells, but are nevoid tumors (hamartomas) derived from arrested embryonal primary epithelial germ cells. They represent the least differentiated group of primary epithelial germ tumors. In my classification of the primary epithelial germ tumors they are grouped as nonorganic hamartomas (table in part I).[1] The name basal cell epithelioma has been retained in spite of my belief that basal cell epitheliomas do not originate from basal cells, because its use is so well established. The designation basal cell carcinoma should, however, be avoided.

The proposition that basal cell epitheliomas are not carcinomas is based on the fact that they probably never metastasize.

Niles [2] stated that metastasis of a pure basal cell epithelioma to a lymph node was an extremely rare event. In a thorough search through the literature up to 1931 he found only 5 histologically proved cases. Broders,[3] in his study of about 6,000 cases of cutaneous epithelioma, did not find a single case of metastatic basal cell epithelioma. Montgomery,[4] in 1935, concluded that basal cell epitheliomas did not

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Dr. Tracy B. Mallory and Dr. Benjamin Castleman, Boston, and Dr. Fred D. Weidman, Philadelphia, gave advice and made valuable suggestions.

1. Lever, W. F.: Pathogenesis of Benign Tumors of Cutaneous Appendages and of Basal Cell Epithelioma: I. Benign Tumors of the Cutaneous Appendages, to be published.

2. Niles, H. D.: Metastasis of a Basal Cell Epithelioma: Report of a Case with the Histologic Picture of a Basal Cell Epithelioma and the Clinical Course of a Squamous Cell Epithelioma, Am. J. Cancer **15**:2341, 1931.

3. Broders, A. C., cited by Montgomery.[4]

4. Montgomery, H.: Basal Squamous Cell Epithelioma, Arch. Dermat. & Syph. **18**:50 (July) 1928.

metastasize as such. Walther [5] expressed the belief that cases of metastasizing basal cell epithelioma occasionally reported in the literature represented wrong diagnoses.

The presence of even numerous mitotic figures in basal cell epithelioma is no evidence of malignancy. The number of mitotic figures in any lesion is an indication only of the rate of cell multiplication. It is common knowledge that numerous mitotic figures can be observed in benign lesions showing active growth, as, for instance, in condylomata acuminata.[6]

The proposition that basal cell epitheliomas do not originate from basal cells is based on the following two reasons:

1. The cells of basal cell epithelioma do not have intercellular bridges, whereas basal cells do.[7] Since basal cells have intercellular bridges, all tumors arising from basal cells, except for the most immature, should have intercellular bridges.

Haythorn [7c] was able to demonstrate intercellular bridges between basal cells in every instance in which the specimens were subjected to immediate fixation in Zenker's fluid and were stained with phosphotungstic acid hematoxylin.

2. No essential difference exists between basal cells and squamous cells. The squamous cell represents merely a stage in the development of the basal cell into a cornified cell. Thus, it appears unlikely that basal cells and squamous cells can give rise to two types of tumors as different as basal cell epithelioma and squamous cell carcinoma.

Hoepke [7b] suggested the use of the term stratum germinativum for the squamous cell layers as well as the basal cell layer, because regeneration, as evidenced by the presence of mitoses, occurs throughout these layers. He stated that the separate position of the basal cells could not be maintained since they differed from squamous cells only by their cylindric shape.

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5. Walther, H. E.: Untersuchungen über Krebsmetastasen: IV. Die Metastasen der Hautkrebse und die sekundären Geschwülste der Haut, Schweiz. med. Wchnschr. **71**:998, 1941.

6. Montgomery, H.: Precancerous Dermatosis and Epithelioma in Situ, Arch. Dermat. & Syph. **39**:387 (March) 1939.

7. (*a*) Pinkus, F.: Die normale Anatomie der Haut, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol. 1, pt. 1, pp. 87 and 116. (*b*) Hoepke, H.: Die Haut, in von Möllendorf, W.: Handbuch der mikroskopischen Anatomie des Menschen, ibid., 1927, vol. 3, pt. 1, pp. 4 and 77. (*c*) Haythorn, S. R.: Studies on the Histogenesis of the So-Called "Basal Cell Carcinoma," Am. J. Cancer **15**:1969, 1931. (*d*) Beck, S. C.: Epithelioma, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1933, vol. 12, pt. 3, p. 254. (*e*) Pernkopf, E., and Patzelt, V.: Anatomie und Histologie der Haut, in Arzt, L., and Zieler, K.: Die Haut- und Geschlechtskrankheiten, Berlin, Urban & Schwarzenberg, 1934, vol. 1, p. 33. (*f*) Montgomery, H.: Histogenesis of Basal Cell Epithelioma, Radiology **25**:8, 1935.

The proposition that basal cell epitheliomas are nevoid tumors (hamartomas) is based on the following facts:

1. Basal cell epitheliomas cannot be produced experimentally. Experimentally produced carcinomas of the skin always are squamous cell carcinomas.[8]

2. Basal cell epitheliomas may occur in large number, widely distributed over the skin, without provocation by a carcinogenic agent. Nomland,[9] Pautrier and Archambault[10] and Nisbet[11] described cases with more than a hundred basal cell epitheliomas. Multiple basal cell epitheliomas on the trunk and the extremities often are superficial. Wise,[12] Montgomery[13] and other American authors have described basal cell epitheliomas of this type under the name "multiple superficial epitheliomatosis," while in the German literature the name "carcinoids" has usually been employed.

The development of most basal cell epitheliomas late in life is not at variance with the assumption that they are nevoid tumors. Several types of nevoid tumors of the skin, such as capillary hemangiomas, fibromas, and keratoses seborrheicae (verrucae seniles), develop at advanced age.

The view that basal cell epitheliomas are nevoid tumors is not at all original. Jesionek,[14] in 1916, included certain basal cell epitheliomas in the nevoid group of tumors with epithelioma adenoides cysticum, adenoma sebaceum, hidradenoma and similar tumors, but called the rodent ulcer a carcinoma because of the inflammatory reaction which it produced and which he regarded as an essential process in the formation of cancer. Hoffmann and Frieboes[15] stated, without amplification, that there were many facts which suggested that basal cell epithelioma was a nevoid tumor. Glasunow[8] expressed the belief that basal cell

8. Glasunow, M.: Ueber das Wesen und die Histogenese des sogenannten Basalzellenkrebses, Frankfurt. Ztschr. f. Path. **46**:140, 1933.

9. Nomland, R.: Multiple Basal Cell Epitheliomas Originating from Congenital Pigmented Basal Cell Nevi, Arch. Dermat. & Syph. **25**:1002 (June) 1932.

10. Pautrier, L. M., and Archambault, G.: Cas extraordinaire d'épithéliomatose cutanée multiple, Bull. Assoc. franç. p. l'étude du cancer **16**:835, 1927.

11. Nisbet, T. W.: Multiple Basal Cell Epitheliomas Originating from Congenital Pigmented Basal Cell Nevi, Arch. Dermat. & Syph. **47**:373 (March) 1943.

12. Wise, F.: Multiple Superficial Benign Epithelioma of the Skin, Arch. Dermat. & Syph. **19**:1 (Jan.) 1929.

13. Montgomery, H.: Superficial Epitheliomatosis, Arch. Dermat. & Syph. **20**:339 (Sept.) 1929.

14. Jesionek, A.: Biologie der gesunden und kranken Haut, Leipzig, F. C. W. Vogel, 1916, pp. 181 and 628.

15. Hoffmann, E., and Frieboes, W.: Zur Kenntnis der Schweissdrüsennaevi mit besonderer Berücksichtigung des Naevus syringadenomatodes papilliferus und Bemerkungen über epitheliale Naevi, Dermat. Ztschr. **27**:255, 1919.

epitheliomas were dysontogenetic tumors. He regarded imperfections in the closure of the embryonal facial fissures as an important etiologic factor, because the majority of basal cell epitheliomas were located in the vicinity of the facial fissures. He concluded that basal cell epitheliomas arose from "isolated cell groups of the embryonal ectoderm" and were tumors of embryonal basal cells, not of mature basal cells. He preferred the name carcinoid to basal cell carcinoma. McFarland, Ciccone and Gelehrter [16] confirmed Glasunow's observation regarding the distribution of basal cell epitheliomas on the face and shared his conclusions. Arning,[17] Kyrle,[18] Fuhs, [19] Schmidt [20] and Wise [12] regarded the multiple superficial epitheliomas as nevoid tumors. The close relationship of these tumors to frank basal cell epithelioma is generally conceded.

The proposition that basal cell epitheliomas originate from the primary epithelial germ is based on the following facts:

1. Basal cell epitheliomas occur only in areas where primary epithelial germ structures (hair, sebaceous or apocrine glands) are found, namely, on the skin, with the exception of the palms and soles where primary epithelial germ structures are absent.

2. The cells of undifferentiated basal cell epitheliomas resemble the cells of primary epithelial germs as seen in the stratum germinativum during the third to fourth month of embryonal life (fig. 1). Both differ from basal cells by the absence of intercellular bridges and the appearance of their nuclei, which are longer, more closely packed and more basophilic.

Von Albertini [21] likened the appearance of early basal cell epithelioma to "embryonal hair proliferations," and Adamson [22] likened it to "embryonal pilo-sebaceous follicles."

3. Structures resembling sebaceous glands, tubular glands and hair are seen in many basal cell epitheliomas. The presence of these struc-

16. McFarland, J.; Ciccone, E. F., and Gelehrter, J.: On the Dysontogenetic Origin of Basal Cell Carcinoma, Am. J. Cancer **25**:273, 1935.

17. Arning: Ein Fall von multiplen Carcinoiden der Haut, Arch. f. Dermat. u. Syph. **138**:458, 1922.

18. Kyrle, J., in the discussion on Arning.[17]

19. Fuhs, H.: Ueber die multiplen Carcinoide der Haut, Acta dermat.-venereol. **7**:233, 1926.

20. Schmidt, F.: Zur Kenntnis der multiplen Karzinoide der Haut, Dermat. Ztschr. **48**:275, 1926.

21. von Albertini, A.: Zur Histogenese der Basaliome, Schweiz. med. Wchnschr. **71**:992, 1941.

22. Adamson, H. G.: Epithelioma Adenoides Cysticum of Brooke in Mother, Daughter and Two Sons, Associated with So-Called "Multiple Endotheliomas of the Scalp": Its Relationship to Multiple Rodent Ulcer, Proc. Roy. Soc. Med. **7**:95, 1913-1914.

tures may be explained on the basis of beginning differentiation of primary epithelial germ cells toward sebaceous glands, apocrine glands and hair.

4. Basal cell epitheliomas may be present in the same lesion with nevus sebaceus, syringocystadenoma papilliferum, sebaceous epithelioma or trichoepithelioma. Furthermore, tumors showing an intermediate

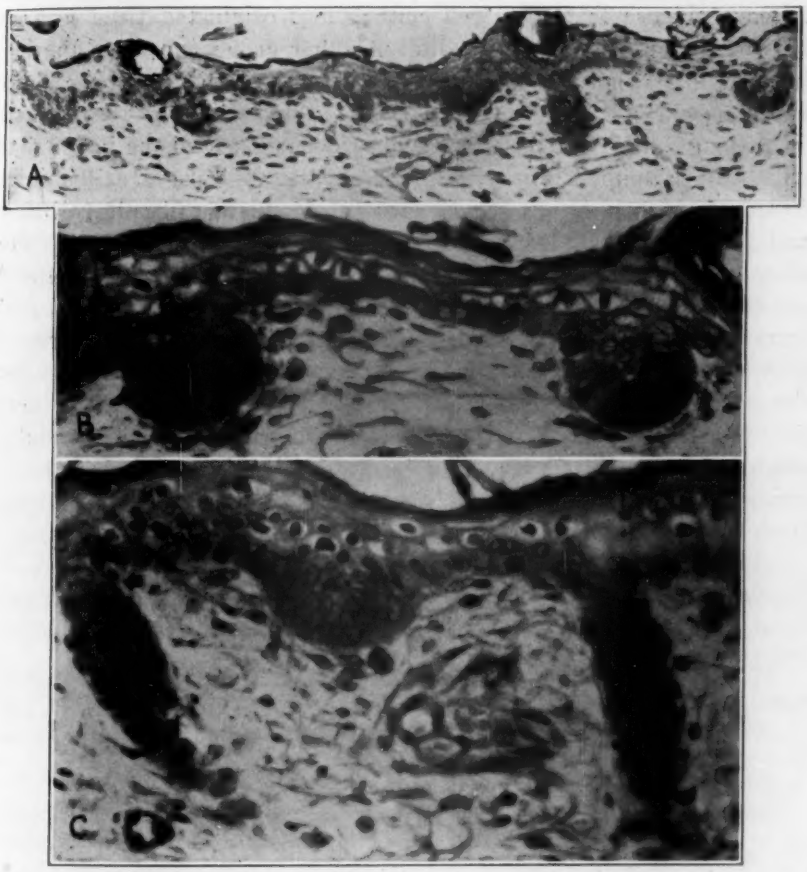

Fig. 1.—Skin of an embryo, 4 months old. *A*, six primary epithelial germs in an early stage of development. Their cells resemble those seen in undifferentiated basal cell epithelioma. *B*, two primary epithelial germs are shown. They are slightly more highly developed than those in *A*. *C*, two of the three primary epithelial germs have proliferated deeply into the corium.

stage of differentiation between basal cell epithelioma and any one of the benign epitheliomas occur, and instances of transformation of lesions of trichoepithelioma into basal cell epithelioma have been reported. These observations, already cited when the respective tumors were discussed, indicate a close relationship between basal cell epi-

thelioma and these tumors and suggest a common origin. Since I regard the primary epithelial germ as the origin of nevus sebaceus, syringocystadenoma papilliferum and the benign epitheliomas, I believe that the primary epithelial germ gives rise also to basal cell epithelioma.

The question as to the structure from which basal cell epithelioma develops has frequently been discussed in the literature. Many authors have previously noted the presence of sebaceous, tubular and hair structures in basal cell epitheliomas. One group of authors regarded this as evidence that basal cell epitheliomas originated from mature cells of the cutaneous appendages. Another group expressed the belief that they originated from those basal cells which formed the cutaneous appendages.

Among authors of the first group, Coenen [23] stated the belief that all basal cell epitheliomas originated from the appendages of the skin, from either the sebaceous glands, sweat glands or hair sheaths. Ricker and Schwalb [24] regarded the sebaceous and sweat glands as the site of origin for all basal cell epitheliomas. Darier [25] and Lacassagne [26] stated the belief that at least some basal cell epitheliomas originated from hair follicles, sebaceous glands and sweat glands. Pautrier [27] expressed the thought that many basal cell epitheliomas arose from the cells at the neck of sebaceous glands. Warren, Gates and Butterfield [28] assumed that some basal cell epitheliomas were of glandular origin. Mallory [29] and Haythorn [7c] regarded basal cell epitheliomas as tumors of the hair matrix and Nicolas and Favre [30] as tumors arising from the hair sheaths.

Among authors of the second group, Krompecher [31] expressed, in his first description of the basal cell carcinoma in 1900, the belief that basal cell carcinomas which showed a tendency to gland formation

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23. Coenen, H.: Die geschichtliche Entwicklung der Lehre vom Basalzellenkrebs, Berl. klin. Wchnschr. **44**:662, 1907.

24. Ricker, G., and Schwalb, J.: Die Geschwülste der Hautdrüsen, Berlin, S. Karger, 1914.

25. Darier, J., in discussion on Masson and Géry.[30]

26. Lacassagne: Répartition des différentes variétés histologiques d'épithéliomas de la peau suivant les régions anatomiques, le sexe et l'age, Ann. de dermat. et syph. **4**:497, 613 and 722, 1933.

27. Pautrier, L. M.: Le naevus sébacé de la face et du cuir chevelu; l'épithelioma sébacé, Ann. de dermat. et syph, **7**:897, 1936.

28. Warren, S.; Gates, O., and Butterfield, P. W.: The Value of Histologic Differentiation of Basal Cell Carcinoma, New England J. Med. **215**:1060, 1936.

29. Mallory, F. B.: Recent Progress in the Microscopic Anatomy and Differentiation of Cancer, J. A. M. A. **55**:1513 (Oct. 29) 1910.

30. Nicolas, J., and Favre, M: Notes cytologiques touchant l'histogénèse des néoplasmes cutanés épithéliaux, Compt. rend. Soc. de biol. **82**:497, 1919.

31. Krompecher, E.: Der drüsenartige Oberflächen-Epithelkrebs. (Carcinoma epitheliale adenoides), Beitr. z. path. Anat. u. z. allg. Path. **28**:1, 1900.

imitated the embryonal gland formation of the basal cells. Ribbert [32] called the basal cell epitheliomas "adenogenous skin carcinomas," because they developed either from the epidermis in the same manner as the cutaneous glands or from the cutaneous glands themselves. Krainz,[33] in a paper dealing with glandlike formations in basal cell carcinomas, stated that the normal epidermis contained, besides basal cells which had the tendency to cornification, also basal cells which developed into glandular cells. He expressed the belief that the latter type of basal cell gave rise to basal cell carcinoma. Similarly, Geschickter and Koehler [34] and von Albertini [21] regarded the basal cell epitheliomas as tumors of those basal cells which formed the cutaneous appendages. Geschickter and Koehler preferred the designation "appendage cell carcinoma" to basal cell carcinoma.

It appears unlikely to me that basal cell epitheliomas originate from any single member of the cutaneous appendages, because in many basal cell epitheliomas with evidence of differentiation sebaceous, tubular and hair structures are present simultaneously and, as a rule, no connections with any of the cutaneous appendages are observed. The theory that basal cell epitheliomas originate from those basal cells which form the cutaneous appendages approaches the theory offered in this presentation, but differs in that, in this presentation, basal cell epitheliomas are not regarded as carcinomas, the cells which form the cutaneous appendages are not regarded as basal cells and the tubular structures are regarded as apocrine rather than as eccrine sweat gland structures.

One author closely approached the view taken in this presentation: Adamson [35] regarded the basal cell epitheliomas as nevoid tumors originating from "latent embryonic foci aroused from their dormant state at a later period of life." He stated the belief that the latent embryonic foci usually were embryonic pilosebaceous follicles, but occasionally were embryonic sweat ducts. The only difference between

32. Ribbert, H.: Das Karzinom des Menschen, Bonn, F. Cohen, 1911, p. 37.

33. Krainz, W.: Ueber drüsenartige Bilder bei Basalzellenkrebsen, Dermat. Wchnschr. **73**:1297, 1921.

34. Geschickter, C. F., and Koehler, H. P.: Ectodermal Tumors of the Skin, Am. J. Cancer **23**:804, 1935.

35. Adamson, H. G.: Two Cases of Multiple Rodent Ulcer; with a Note on the Possible Relationship Between Multiple Rodent Ulcer and Epithelioma Adenoides Cysticum of Brooke, Lancet **2**:1133, 1908; On the Nature of Rodent Ulcer: Its Relationship to Epithelioma Adenoides Cysticum of Brooke and to Other Tricho-Epitheliomata of Benign, Nevoid Character; Its Distinction from Malignant Carcinoma, ibid. **1**:810, 1914; in discussion on Little, E.G.G.: A Case for Diagnosis: (?) Multiple Rodent Ulcer or Epithelioma Adenoides Cysticum, Brit. J. Dermat. **27**:20, 1915; Case of Multiple Superficial Rodent Ulcer: Possible Embryonic Sweat-Duct Origin, Proc. Roy. Soc. Med. **16**:24, 1922-1923. Footnote 22.

Adamson's view and the view taken in this presentation is that Adamson regarded the tubular structures in basal cell epithelioma as eccrine while in this presentation they are regarded as apocrine. It must be realized, however, that Adamson's work preceded Schiefferdecker's original description of the apocrine glands.

Theoretically, the possibility must be considered that some basal cell epitheliomas with differentiation only to tubular structures are not primary epithelial germ hamartomas but eccrine sweat gland hamartomas. Whether or not this is actually the case is difficult to decide, because the tubular formations in basal cell epitheliomas do not show sufficient differentiation to allow a decision as to whether they are apocrine or eccrine. However, most basal cell epitheliomas with evidence of differentiation to tubular formations show differentiation also to sebaceous and hair structures. Furthermore, basal cell epitheliomas have never been described as occurring on the palms and soles, where eccrine glands are most numerous.

In this paper, the basal cell epitheliomas are divided into two main groups: undifferentiated and differentiated, the latter showing differentiation toward primary epithelial germ structures. A sharp dividing line between the two groups cannot be drawn, because many undifferentiated basal cell epitheliomas show in some areas differentiation and most differentiated basal cell epitheliomas show areas lacking differentiation.

DIFFERENTIATED BASAL CELL EPITHELIOMAS

The basal cell epitheliomas with differentiation toward sebaceous glands are called cystic in this thesis; those with differentiation toward apocrine glands are called adenoid, and those with differentiation toward hair are called keratotic basal cell epithelioma. This division corresponds to Krompecher's original classification.[36]

Cystic Basal Cell Epithelioma.—Cystic spaces are present in the center of cell masses (fig. 2). The cells in the vicinity of the cysts often contain, as already Ribbert [37] has pointed out, foamy cytoplasm similar to that seen in sebaceous cells. I believe that they are cells with beginning differentiation toward sebaceous cells, i. e., transitional cells of Grynfeltt.[38] The cystic spaces are formed by cellular disintegration which is analogous to the disintegration of sebaceous cells in the process of forming their secretion.

Adenoid Basal Cell Epithelioma.—Adenoid basal cell epithelioma is a type of tumor which shows formations suggesting tubular gland

36. Krompecher, E.: Der Basalzellenkrebs, Jena, Gustav Fischer, 1903, p. 6.

37. Ribbert,[32] p. 43.

38. Grynfeltt, E.: Un cas d'épithélioma baso-sébacé, Bull. Assoc. franç. p. l'étude du cancer **13**:474, 1924.

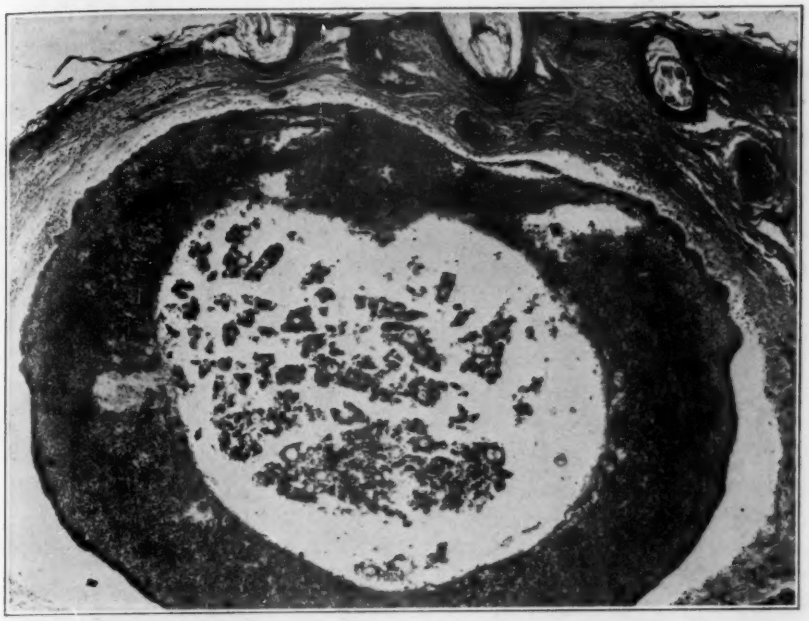

Fig. 2.—Cystic basal cell epithelioma. The cyst has formed by disintegration of "transitional" cells.

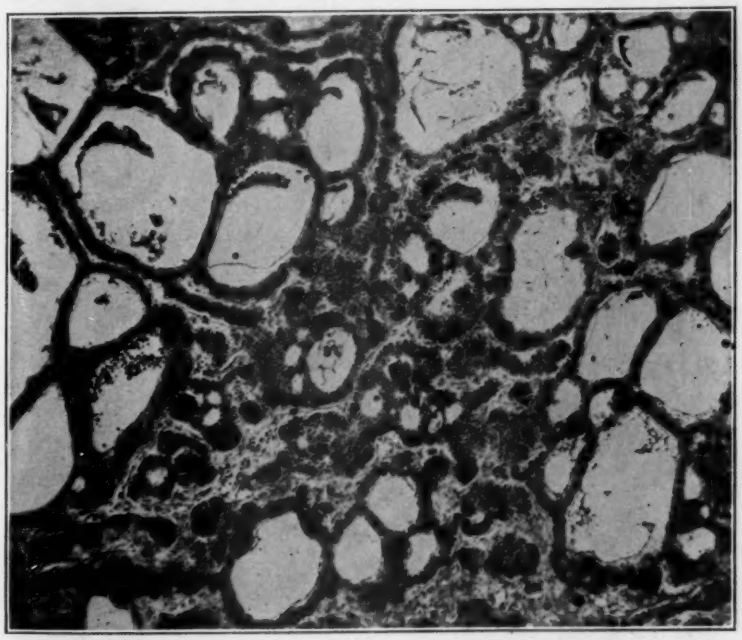

Fig. 3.—Adenoid basal cell epithelioma. The cells are in part arranged around glandular lumens.

structures. The cells are arranged in intertwining strands and radially around islands of connective tissue, resulting in a "lacelike" patterning of the tumor. Occasionally, lumens are present surrounded by cells which have the appearance of glandular cells (fig. 3). The cells show, however, no definite evidence of active secretion into the lumens, so that it is impossible to conclude from the appearance of the cells whether they are of apocrine or eccrine origin.

Keratotic Basal Cell Epithelioma.—In the keratotic basal cell epithelioma, cells with elongated nuclei and eosinophilic cytoplasm are

Fig. 4.—Keratotic basal cell epithelioma. No prickle cells are present.

seen in concentric arrangement around keratotic or parakeratotic centers (fig. 4). Frequently, groups of similar cells traverse the tumor as short bands (fig. 5). These cells have the appearance of hair matrix cells and are regarded as primary epithelial germ cells which have differentiated toward hair matrix cells. The presence of these cells induced Mallory [20] and Haythorn [7c] to conclude that many basal cell epitheliomas were hair matrix tumors. Just as normally the keratotic hair cells develop from hair matrix cells, so the keratotic cells in keratotic basal cell epithelioma develop from hair matrix cells and not from prickle cells. Some keratotic basal cell epitheliomas show

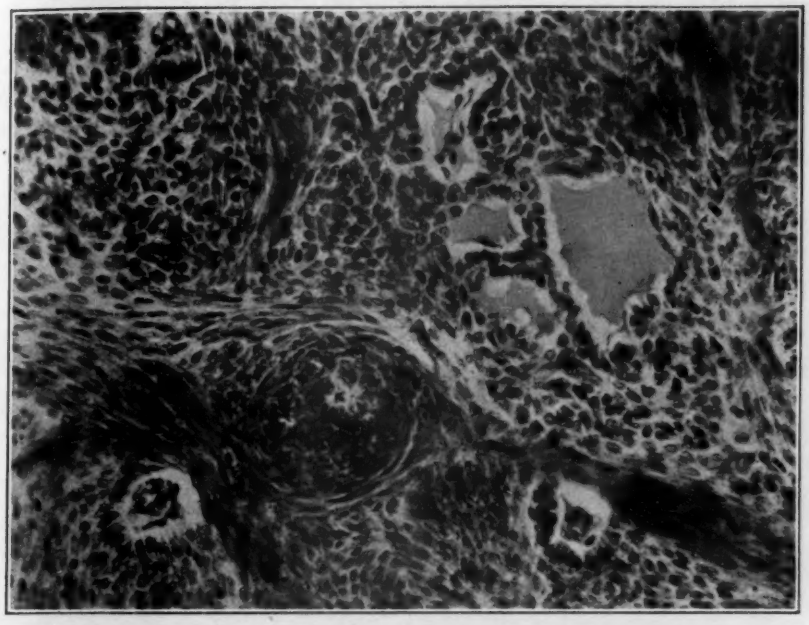

Fig. 5.—Basal cell epithelioma showing differentiation into hair matrix and keratotic cells in some areas and differentiation into adenoid structures in others.

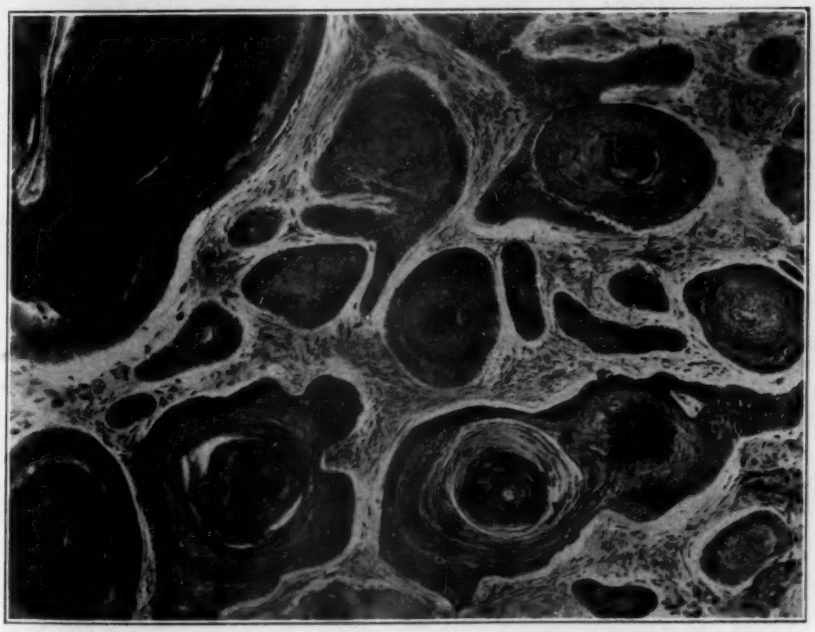

Fig. 6.—Keratotic basal cell epithelioma with large "horn cysts."

areas in which keratinization has progressed to the formation of keratotic "cysts" similar to those observed in trichoepithelioma (fig. 6). The presence of keratotic cells should not be regarded as evidence of "basal squamous cell epithelioma" or "mixed carcinoma," as some authors have suggested, because keratinization is one of the potentialities of primary epithelial germ cells.

In most differentiated basal cell epitheliomas differentiation is directed toward more than one of the three structures developing from the primary epithelial germ. For example, areas of keratinization may be seen in a tumor which also shows glandular structures (fig. 5).

Not infrequently, tumors showing a transitional stage of differentiation between differentiated basal cell epithelioma and benign epithelioma are observed. For instance, some cystic basal cell epitheliomas approach, in their appearance, that of sebaceous epithelioma by showing beginning differentiation into transitional and sebaceous cells; some adenoid basal cell epitheliomas show, in addition to tubular formations, myoepithelial cells and thus resemble myoepithelioma, and some keratotic basal cell epitheliomas, due to the presence of well developed "horn cysts," resemble trichoepithelioma.

UNDIFFERENTIATED BASAL CELL EPITHELIOMAS

The undifferentiated basal cell epitheliomas are tumors which originate, in my opinion, from primary epithelial germ cells which possess little or no power of organization and differentiation but power of multiplication. They are, therefore, composed essentially of undifferentiated primary epithelial germ cells. This group includes the solid basal cell epithelioma, the pigmented basal cell epithelioma, the basal cell papilloma and the superficial basal cell epithelioma.

Solid Basal Cell Epithelioma.—The solid basal cell epithelioma is composed of large and small clusters of cells. The peripheral cell layer of each cluster usually shows palisade arrangement. The nuclei are elongated, closely packed and deeply basophilic.

Some basal cell epitheliomas with little or no structural differentiation toward the cutaneous appendages show, nevertheless, evidence of cellular differentiation by presenting two types of cells. One type of cell has small elongated deeply basophilic nuclei, and the other has large round less basophilic granular nuclei. The former are regarded as cells differentiating toward either myoepithelial cells of apocrine glands or hair matrix cells, and the latter are regarded as cells differentiating toward secretory cells of either sebaceous or apocrine glands (fig. 7.)

Darier,[39] Montgomery [4] and Juon [40] have described so-called intermediary or transitional cell carcinomas in which two types of cells occur, namely, cells with small elongated deeply basophilic nuclei, regarded by them as "basal cells," and cells with large round granular nuclei, regarded by them as "intermediary in character between basal and prickle cells." These authors concluded that the tumors were intermediary between basal cell and squamous cell carcinoma. I believe that the "intermediary carcinoma" is identical with the just described type of basal cell epithelioma in which the cells show beginning differentiation toward the various kinds of cells into which primary epithelial germ cells may develop. I doubt the existence of tumors which are intermediary between basal cell epithelioma and squamous cell carcinoma.

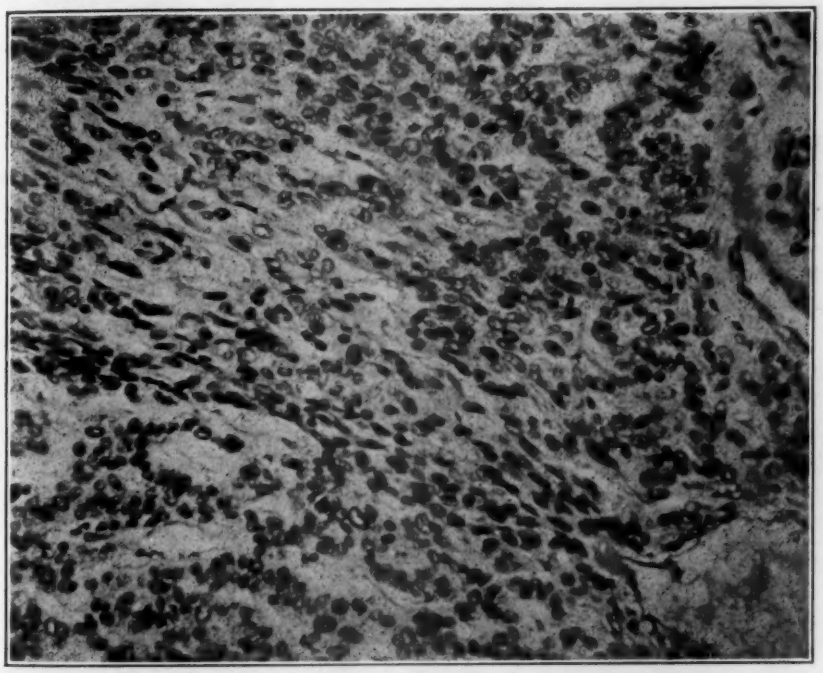

Fig. 7.—Basal cell epithelioma with differentiation into two types of cells. One type of cell has large oval pale nuclei, and the other type has small elongated darkly staining nuclei. The majority of cells are of the former type.

Pigmented Basal Cell Epithelioma.—Although the presence of pigment can be demonstrated by special staining methods in many basal

39. Darier, J., and Ferrand, M.: L'épithéliome pavimenteux mixte et intermédiaire, Ann. de dermat. et syph. **3**:385, 1922.

40. Juon, M.: Ueber die "metatypischen" Formen der Hautepitheliome, Arch. f. Dermat. u. Syph. **157**:81, 1929.

cell epitheliomas,[41] large amounts are only rarely encountered. Two types of epidermal cells have the ability of forming melanin, the basal cells of the epidermis and hair matrix cells. I believe that the melanin-bearing cells in basal cell epitheliomas are hair matrix cells. Basal cell epitheliomas with large amounts of pigment usually contain interspersed between the tumor cells dendritic cells filled with pigment.[42] Their presence can be explained by the fact that dendritic cells develop in normal hair directly above the papilla interspersed between the hair matrix cells.

Basal Cell Papilloma or Keratosis Seborrheica, also Called Verruca Senilis, and Papilloma Senile.—The term basal cell papilloma is suggested for tumors showing a combination of papilloma (nevus verrucous) and epithelial hyperplasia. Epithelial hyperplasia designates, according to Becker,[43] areas of epidermal thickening composed not of squamous cells, as areas of acanthosis are, but of cells of the same type as seen in undifferentiated basal cell epithelioma. Thus, the cells in areas of epithelial hyperplasia do not possess prickles, while those in areas of papilloma do. Clinically, basal cell papillomas manifest themselves either as seborrheic senile verrucae or as senile papillomas, the difference being one of size only.[44]

Although basal cell papillomas show but little tendency to invasion of the corium, they are to be regarded as a variety of basal cell epithelioma under the terminology and conditions of the primary epithelial germ concept which is the basis in this paper. The majority of cells in these tumors are of the same type as seen in solid basal cell epithelioma. Additional points of similarity are: Areas of solid downward proliferation may contain no prickle cells and thus resemble superficial basal cell epithelioma; in other areas the downward proliferation may be in the form of a network of epithelial strands, just as in adenoid basal cell epithelioma, and horn cysts, identical with those observed in keratotic basal cell epithelioma and trichoepithelioma, are frequently present.[45]

41. Becker, S. W.: Pigmented Epitheliomas, Arch. Dermat & Syph. **27**:981 (June) 1933.

42. Bloch, B.: Ueber benigne, nicht naevoide Melanoepitheliome der Haut nebst Bemerkungen über das Wesen und die Genese der Dendritenzellen, Arch. f. Dermat. u. Syph. **153**:20, 1927.

43. Becker, S. W.: Benign Epidermal Neoplasms, Arch. Dermat. & Syph. **26**:838 (Nov.) 1932.

44. (*a*) Becker.[43] (*b*) Kreibich, C.: Granuloma senile, Arch. f. Dermat. u. Syph. **153**:107, 1927. (*c*) Hookey, J. A.: Keratoma Senile and Verruca Senilis, Arch. Dermat. & Syph. **23**:946 (May) 1931. (*d*) Montgomery, H., and Dörffel, J.: Verruca senilis und Keratoma senile, Arch. f. Dermat. u. Syph. **166**:286, 1932.

45. (*a*) Hookey.[44c] (*b*) Montgomery.[44d] (*c*) Eller, J. J., and Ryan, V. J.: Senile Keratoses and Seborrheic Keratoses, Arch. Dermat. & Syph. **22**:1043 (Dec.) 1930. (*d*) Freudenthal, W.: Verruca senilis und Keratoma senile, Arch. f. Dermat. u. Syph. **152**:505, 1926.

Actual change, however, of basal cell papilloma into a frank basal cell epithelioma with deep invasion and ulceration is rare.[46] Some authors have even denied this occurrence. It is my belief, however, that if active growth occurs in a basal cell papilloma the newly formed primary epithelial germ cells may have greater invasive power than the older cells and that thus a lesion of epithelial hyperplasia may change into a frank basal cell epithelioma. This is an occurrence similar to the rare transformation of trichoepithelioma into basal cell epithelioma.

Pathogenetically, basal cell papilloma is regarded as a hamartoma originating from primary epithelial germ cells as well as embryonal surface epidermis cells. Most basal cell papillomas show pigmentation in various degrees. The pigment usually is observed in the tumor cells, but occasionally dendritic cells containing pigment are present.[47]

Superficial Basal Cell Epithelioma.—Superficial basal cell epithelioma is a type of tumor which originates from the epidermis in multiple foci and shows little penetration into the corium. Occasionally, superficial epitheliomas show areas of hyperkeratosis and papilloma formation. In those areas, prickle cells are seen. Their presence should not be regarded as evidence of "mixed carcinoma," but as evidence of "mixed hamartoma" originating from primary epithelial germ cells and embryonal surface epidermis cells.

"Mixed Carcinomas."—"Mixed carcinomas" are tumors showing a squamous cell carcinoma contiguous to a basal cell epithelioma. I believe that in most instances of "mixed carcinoma" the squamous cell carcinoma develops secondary to the basal cell epithelioma. Basal cell epithelioma, like other chronic lesions, for instance lupus vulgaris, lupus erythematosus, gumma and burns, may stimulate the development of a squamous cell carcinoma.

SUMMARY

Several groups of cutaneous tumors originate from the primary epithelial germ.

Primary epithelial germs begin to appear in the embryonal stratum germinativum during the third and fourth month of embryonal life. They differentiate into sebaceous glands, apocrine glands and hair. Tumors arising from primary epithelial germ cells, therefore, show various degrees of differentiation toward sebaceous glands, apocrine glands and hair.

46. Eller and Ryan.[45e] Waelsch, L.: Ueber die Verruca senilis und die aus ihr entstehenden Epitheliome, Arch. f. Dermat. u. Syph. **76**:31, 1905. Cipollaro, A. C.: Seborrheic Keratosis with Epithelioma, Arch. Dermat. & Syph. **48**:567 (Nov.) 1943.

47. Hookey.[44c] Montgomery.[44d] Becker, S. W.: Cutaneous Melanoma, Arch. Dermat. & Syph. **21**:818 (May) 1930.

Since the primary epithelial germ is an embryonal structure, tumors arising from it are nevoid tumors (hamartomas).

The type of tumor depends on the degree and direction of differentiation in the primary epithelial germ cells prior to the onset of neoplasia. More highly differentiated primary epithelial germ cells give rise to more highly differentiated tumors.

The primary epithelial germ tumors may be divided, according to the decreasing degree of organization and differentiation, into four groups: organic hamartomas (nevi organomatosi), organoid hamartomas (adenomas), suborganoid hamartomas (benign epitheliomas) and non-organic hamartomas (basal cell epitheliomas). Each of the four groups may be subdivided, according to the direction of differentiation, into hamartomas with differentiation toward sebaceous gland, apocrine gland and hair structures.

Although in all tumors the differentiation is directed mainly toward one primary epithelial germ structure, many show, in addition, differentiation toward the other two primary epithelial germ structures. The occurrence of transitional forms between the various tumors and of combinations of two or more varieties of primary epithelial germ tumors in the same patient and even in the same lesion is evidence of the close relationship between the tumors arising from the primary epithelial germ.

Basal cell epitheliomas are not considered carcinomas because they do not metastasize. Their origin from basal cells is doubted because their cells, in contrast to basal cells, do not possess intercellular bridges. Basal cell epitheliomas are regarded as hamartomas because they cannot be produced experimentally and frequently are multiple. They are believed to originate from the primary epithelial germ for the following reasons: They occur only in areas where primary epithelial germ structures (sebaceous glands, apocrine glands or hair) are seen; the cells of undifferentiated basal cell epitheliomas resemble the cells of primary epithelial germs; structures resembling sebaceous glands, tubular glands and hair are present in many basal cell epitheliomas, and basal cell epitheliomas are frequently seen in the same lesion with primary epithelial germ tumors of higher differentiation.

Clinical Notes

DERMATOMYOSITIS ASSOCIATED WITH HYPERTRICHOSIS

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Because of its extreme rarity it was deemed worth while to report this case of dermatomyositis associated with hypertrichosis. Dermatomyositis is a rare disease characterized by a nonsuppurative inflammation and degeneration of the striated musculature and associated with diverse cutaneous changes and vasomotor signs similar to Raynaud's phenomenon. It is frequently unrecognized because of its variable clinical manifestations. The disease may have an acute or insidious onset, with frequent remissions and exacerbations, but is eventually fatal in about half the cases. There is no sex predominance, and the age range is usually between 10 and 50 years.[1]

Cutaneous changes [2] are prevalent and include erythema, edema, pigmentation, sclerosis, atrophy, lupus erythematosus-like efflorescence and poikiloderma atrophicans vasculare. Keil [3] minutely described the cutaneous and mucomembranous lesions. However, the microscopic changes are not considered specific for this disorder.[1]

Muscular involvement may produce pain, tenderness, stiffness and fatigue. Serious outcome may be inevitable if the muscles of deglutition or respiration are affected. Although the kidney may be involved, cardiac muscle does not become diseased.[4] Any changes that may be recorded on the electrocardiogram are mainly due to peripheral cutaneous changes affecting conduction (fig. 2).

The question of a common denominator in such vaguely understood diseases as dermatomyositis, scleroderma, disseminated lupus erythematosus, Libman-Sacks syndrome, polyarteritis nodosa and other nosologically related diseases persists. The disease is most frequently confused with glomerulonephritis, lupus erythematosus, myasthenia gravis, pellagra, trichinosis, adrenal disease, diffuse scleroderma, scleredema adultorum and sclerema neonatorum.[5]

At the time of writing Dr. Reich was a major in the Army, Chief of Medical Service, and Lieutenant Reinhart is Ward Surgeon, General Medical Section, Station Hospital, Fort Sill.

1. Jager, B. V., and Grossman, L. A.: Dermatomyositis, Arch. Int. Med. **73**:271 (April) 1944.

2. O'Leary, P. A., and Waisman, M.: Dermatomyositis, Arch. Dermat. & Syph. **41**:1001 (June) 1940.

3. Keil, H.: The Manifestations in the Skin and Mucous Membranes in Dermatomyositis with Special Reference to the Differential Diagnosis from Systemic Lupus Erythematosus, Ann. Int. Med. **16**:828, 1942.

4. Case Records of the Massachusetts General Hospital, Case 31101, New England J. Med. **232**:286, 1945.

5. Reich, N. E.: Sclerema Neonatorum, Arch. Dermat. & Syph. **45**:342 (Feb.) 1942.

Etiologic studies [2] suggest that the disease may be caused either by bacterial invasion from the blood stream or by toxic action of bacterial products on the musculocutaneous structures. Because of the numerous organisms which have been identified by various observers, the causation is at present unestablished. Extensive laboratory studies reveal no constant abnormality other than spontaneous creatinuria.[1]

There is no known specific treatment. The beneficial results with wheat germ oil in reducing creatinuria [6] is difficult to evaluate, because of intermittent showers of creatine excretion normally. It appeared to have no effect in our case. Other modalities of treatment have included vaccines, aminoacetic acid, oxygen inhalations, sulfonamide drugs and pencillin. The last, in concentrated dosage, also failed to produce improvement in this case.

Although the disease may be associated with alopecia, localized hypertrichosis has been observed rarely.[7] The occurrence of this curious phenomenon may indicate an endocrine origin. The inflammatory element, whether accompanied with erythema of the skin or not, would appear to stimulate growth of hair, possibly through the medium of increased blood supply or the presence of edematous fluid. The following case was characterized by generalized symmetric muscular atrophy and contractures, luxuriant hypertrichosis of the knees, elbows and forehead, creatinuria and eosinophilia.

REPORT OF A CASE

First Admission.—A 9 year old white boy was hospitalized on Sept. 3, 1946, because of increasing weakness. Around June 15 his mother first noticed a mottled rash about the face, with puffiness under the eyes. After a few days he complained of sore throat and sore neck, which was diagnosed as tonsillitis. He was treated with sulfonamide drugs, and the sore throat disappeared but the periorbital puffiness persisted, becoming more apparent in the mornings and evenings. The pain extended from the neck muscles to the back muscles. The pain in the back and neck caused him to cry out. He complained of weakness and had frequent falls the following month. The rash continued to get worse, and the eyes swelled intermittently until they were almost closed. In August he began to complain of pain in the muscles about the hips. His weakness became worse, until he was unable to rise from a sitting position. A complete review of his other systems was noncontributory. He had the usual childhood diseases, without any sequelae. Birth was normal. He had several mild attacks of otitis media, which required no surgical intervention. The family history was noncontributory.

Physical Examination: Examination revealed an underdeveloped, undernourished and chronically ill child. The skin showed edema of the infraorbital regions and circumoral pallor. There was a macular erythematous eruption over the nose, cheeks, chest and abdomen. There was also a confluent depigmentation

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6. Milhorat, A. T.; Toscani, V., and Bartels, W. E.: Effect of Wheat Germ on Creatinuria in Dermatomyositis and Progressive Muscular Atrophy, Proc. Soc. Exper. Biol. & Med. **58**:40, 1945.

7. Keil, H.: Dermatomyositis and Systemic Lupus Erythematosus, Arch. Int. Med. **66**:339 (Aug.) 1940; footnote 3. Schuermann, H.: Zur Klinik und Pathogenese der Dermatomyositis: Polymyositis, Arch. f. Dermat. u. Syph. **178**: 414, 1939. Ingram, J. T., and Stewart, M. J.: Dermatomyositis and Poikilodermia, Brit. J. Dermat. **46**:53, 1934. Peemöller, F.: Ueber Dermatomyositis, Deutsche. Ztschr. f. Nervenh. **68**:370, 1921.

of the interscapular, manubrial and posterior cervical areas. The entire surface of the skin appeared roughened and thickened. Over the elbows and temporal and infrapatellar regions there was a moderate growth of fine long black hairs (fig. 1).

Examination of muscle revealed generalized weakness, especially in the flexor muscles of the neck, hips and legs. The shoulder girdles were decidedly weak. There was no definite atrophy of any muscle groups. His gait was unsteady and

Fig. 1.—*A*, orbital edema, contractures of elbows, knees and fingers, general muscular weakness and depigmentation of the upper part of the chest are illustrated. *B*, areas of depigmentation and pigmentation, hirsutism and brawny induration of lower cervical region and shoulder. *C* and *D*, hirsutism of temporal and infrapatellar regions and atrophy of leg muscles.

"loose." He was unable to arise from a supine position. Neurologic observations were entirely normal, with no sensorial or reflex changes. There was no evidence of spasticity, tremor, ataxia or positive Romberg sign. The muscles of the back and neck and the hamstrings, gastrocnemii and biceps were slightly involved by

apparent fibrotic contractures, since they could not be overcome by passive motion. The spleen was palpable 2 fingerbreadths below the left costal margin. The edge of the liver was enlarged 1 fingerbreadth below the right costal margin. The heart and lungs were entirely normal. The blood pressure was 100 systolic and 70 diastolic. The pulse rate was 90 beats per minute, respirations 20 and temperature 100.2 F.

Laboratory Observations: The hemoglobin was 87.7 per cent, red cell count 3,950,000 and white cell count 7,800, with 40 per cent lymphocytes, 48 per cent mature polymorphonuclear leukocytes, 6 per cent young forms and 6 per cent eosinophils. The sedimentation rate was 17 mm. in one hour (Wintrobe), and the hematocrit reading was 45. Repeated examinations of the stool gave negative

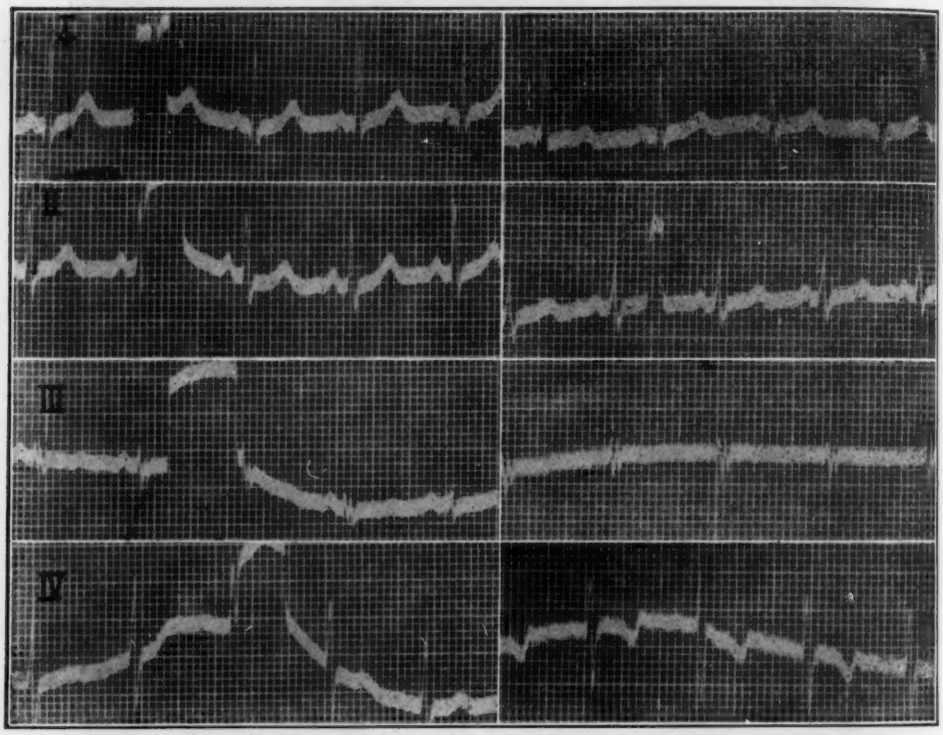

Fig. 2.—Serial electrocardiograms, showing the effect of a severe exacerbation of dermatomyositis. The voltage of T waves has been decreased in the limb leads and inverted in the fourth lead. There are also sinus tachycardia and left axis deviation. These changes are due to variance of cutaneous resistance induced by aggravation of disease and not to myocardial involvement. The electrocardiograms on the left were made on September 18 and those on the right on November 26.

results for ova or parasites. The spinal fluid and the urine were normal. Studies of the chemical content of the blood showed a total serum protein of 7.2 mg. per hundred cubic centimeters, with albumin 5.7 mg. and globulin 1.5 mg. per hundred cubic centimeters. The albumin-globulin ratio was 3.8. Blood cholesterol was 139 mg. per hundred cubic centimeters. A repeated test for total serum protein revealed 6.8 mg. per hundred cubic centimeters. The blood contained 5.7 mg. of phosphorus and 16.6 mg. of calcium per hundred cubic centimeters.

During twenty-four hours 3.9 Gm. of creatinine was excreted in the urine. In another examination, one week later, the amount was 1.08 Gm.

Roentgenograms of the right leg, the chest, the skull and the spine showed no abnormalities except for osteochondrosis (Schlatter-Osgood disease) of the tuberosity of the right tibia. Intravenous pyelographic studies and gastrointestinal

Fig. 3.—Photomicrograph (× 70) of a section of muscle, showing swelling of muscle fibers with loss of striations and fragmentation.

roentgenograms revealed no abnormalities. Electrocardiographic observations were normal on admission (fig. 2).

Clinical Course: He had a low grade fever, up to 100.2 F., during an initial hospital stay of forty days. He complained only slightly of pain in the back and legs after the first few days except when these muscle groups were passively

overstretched. He continued to show decided weakness of all muscles, with gradually increasing contractures. The hair at the temples and infrapatellar regions increased in growth.

Biopsy: A biopsy of the right gastrocnemius was performed September 12. Grossly, the muscle tissue appeared pale and slightly tough, the individual fibers appearing smaller than normal. Microscopic examination (fig. 3 and fig. 4) revealed numerous fragments of skeletal muscle which showed swelling of the

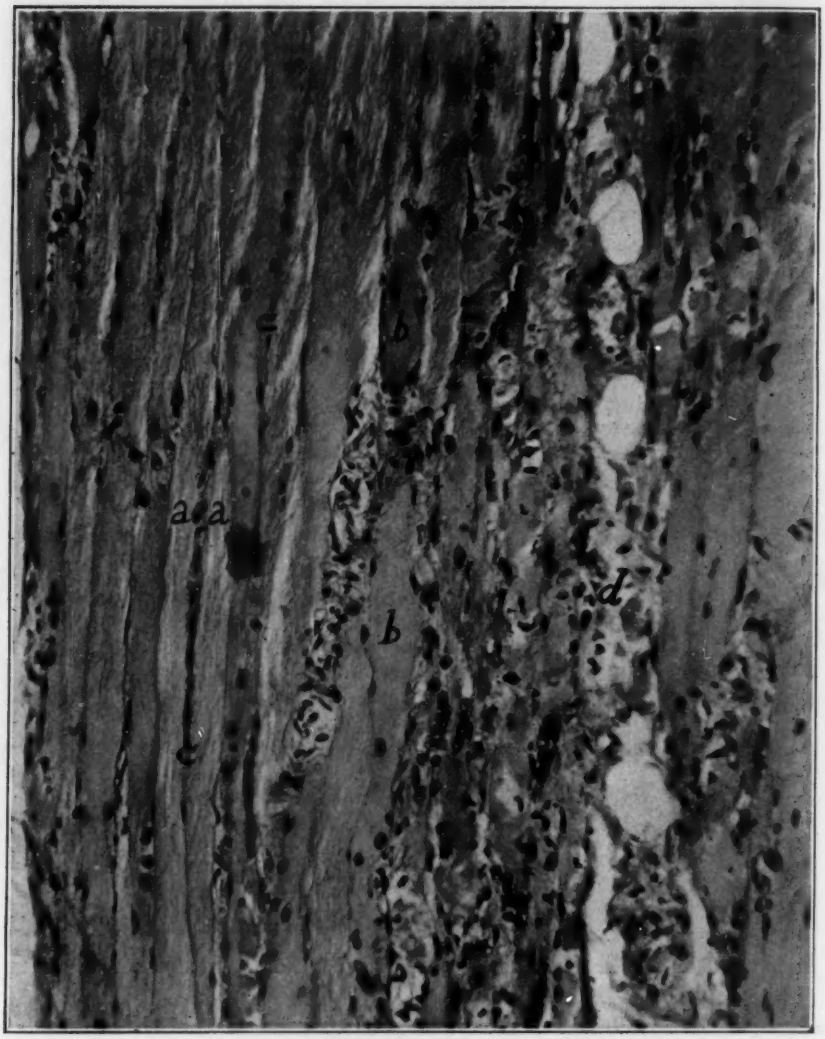

Fig. 4.—Photomicrograph (× 200) of a section of muscle, showing vacuolization (*a*), slight hyaline necrosis (*b*), decided increase in muscle nuclei of the sarcolemma type (*c*) and interstitial infiltration of round cells and occasional plasma and polymorphonuclear cells (*d*). Blood vessel walls are somewhat thickened. There were variations in staining. (Histologic changes in the skin are generally considered as secondary and nonspecific and consist of atrophy of the epidermis, edema and perivascular infiltration of the corium with lymphocytes and plasma cells.)

muscle fibers and loss of striations. There was slight hyaline necrosis and slight increase in interstitial connective tissue. Some of the sections also showed extensive alteration of staining qualities, many of the fibers taking a bluish pink stain. There was decided increase in the muscle nuclei. In some of these areas the abundance of nuclei and the poorly defined borders gave the appearance of giant cells. There was some vacuolization of these fibers. The blood vessels in these areas were dilated, and some had thickened walls. The interstitial spaces presented a slight infiltration of round cells, associated with rare polymorphonuclear cells. There was no evidence of Trichinella spiralis. The general picture was one of degeneration, inflammation, and repair of muscle with interstitial tissue reaction.

Treatment: He was given daily physical therapy, consisting mainly of passive motion. A diet high in caloric content was supplemented with vitamins. There was no appreciable improvement. Alpha tocopherol (50 mg. orally five times daily) was prescribed on discharge.

Second Admission.—He was readmitted on November 1, three weeks after discharge. His mother expressed the belief that he had improved for the first week, but during the second week he again complained of aching in all his muscles and experienced a low grade fever. Increasing contractures were noted by his mother.

Physical Examination: Examination revealed: temperature 100 F., pulse rate 90 and respirations 20. His skin showed greater hypertrichosis of the knees, elbows and temporal regions. The skin was smoother and moister than previously. His face was somewhat improved, and the periorbital tissues did not appear as puffy or erythematous. Examination revealed the lungs and heart to be normal. The spleen was palpable 2 to 3 fingerbreadths below the left costal margin and was firm and nontender. The liver was no more enlarged than previously. There was generalized weakness and more advanced contracture deformities of the arms and legs. The boy was unable to hold his head upright for more than one minute.

Laboratory Studies: The red cell count was 3,650,000 and the white cell count 11,200, with 38 per cent neutrophils, 60 per cent lymphocytes and 2 per cent eosinophils. The hemoglobin was 81 per cent. The urine was normal. Creatinine excretion was 1.06 Gm., compared with 1.08 Gm. and 3.9 Gm. two months previously. This consisted of 0.796 Gm. creatinine and 0.264 Gm. creatine. The creatinine in the blood was 2.18 mg. per hundred cubic centimeters. The sedimentation rate was 48 mm. (corrected to 36 mm.) in one hour, with a hematocrit reading of 41. A repeat examination of the blood on November 26 showed a red cell count of 3,560,000, with 84 per cent hemoglobin, and a white cell count of 12,300, with 62 per cent neutrophils, 24 per cent lymphocytes and 14 per cent eosinophils.

Clinical Course: Because of the reported relationship of this disease to infection (possibly streptococcic), even though hemolytic streptococci were not obtained from throat cultures, penicillin in oil and beeswax mixture was given intramuscularly (300,000 units every day for ten days). Alpha tocopherol was continued throughout the second period of hospitalization. He continued to have a low grade fever, with a peak of 100.4 F. in the afternoon. On November 18 he weighed 51 pounds (23.1 Kg.), a loss of approximately 10 pounds (4.5 Kg.) in three months.

The erythematous macular eruption about the face, legs and trunk became exacerbated. An electrocardiogram (fig. 2) revealed changes suggestive of myocardial damage. Since the heart is uninvolved in dermatomyositis, this was

interpreted as a variance of cutaneous resistance induced by the exacerbation of the cutaneous lesions. The patient was discharged unimproved twenty-four days following the second admission.

SUMMARY AND CONCLUSIONS

An unusual case of dermatomyositis associated with decided hypertrichosis is presented. The increased growth of hair following an exacerbation of the cutaneous lesions suggests an inflammatory origin.

Creatinuria, eosinophilia and generalized symmetric muscular atrophy and contractures were characteristic features.

Physical therapeutic measures and intensive treatment with alpha tocopherol and penicillin were ineffective.

NOTE.—The patient was readmitted to the hospital three months later. In the interim he had received extract of liver, testosterone and physical therapy. A loss of the excess hair had occurred, with replacement by lanugo hair. The inflammatory phase of the cutaneous reaction had subsided. Roentgenograms revealed generalized decalcification of the bones, especially at the epiphysial ends, and decided thinning of the cortices. There was a patchy deposition of calcium throughout the skeletal system, especially involving the gastrocnemius and hamstring muscles and the flexor muscles of the forearm.

41 Eastern Parkway.

TINEA NIGRA IN PANAMA

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During a four year period at the Gorgas Memorial Hospital, Ancon, Canal Zone, from 1942 to 1946, 3 patients were seen with a black fungous infection on the palm. This condition has been described and studied by several Brazilian workers,[1] but has never before been reported from Panama. It is not known to occur in the continental United States. The disease is entirely symptomless and harmless, but deserves reporting as a rare tropical cutaneous disease which is little known and which might be seen in the United States in a soldier or civilian returning from the Panama Canal Zone.

The 3 patients were white North Americans. One was a physician in the Health Department of the Canal Zone; 1 was a clerical worker in one of the Zone offices, and the third was a soldier stationed at an Army fort in the Canal Zone. During the period in which these patients were seen several thousand Panamanians were examined, and although this condition was not specifically looked for it was never noted in them.

None of the 3 patients knew of other persons with the disease, nor had any of them recently visited other parts of Central or South America. The appearance of the black spots was not attributed to any injury or unusual contact. The

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From the Scott and White Clinic.

1. While this report was in preparation, a comprehensive study of this disease was reported (Aroeira Neves, J., and Costa, Oswaldo G.: Tinea Nigra, Arch. Dermat & Syph. **55**:67-84 [Jan.] 1947). For mycologic studies and bibliography, this report should be consulted.

patients could not date a definite time of onset, but the lesions had gradually appeared over a period of several weeks or months. They had observed that by thorough scrubbing with soap and water or by scraping most of the dark color could be removed, but it would gradually reappear in a few days.

The appearance of the disease in 2 of the patients is most accurately described as a superficial silver nitrate stain. They were single lesions, 4 to 6 mm. in diameter, brownish black in color, sharply defined and flat or slightly depressed below the level of the skin. Their location was near the center of the palm, along the "heart line." In the third patient, the skin of the thenar eminence was involved. There were several oval not so well defined areas, the color and appearance of which suggested a faint uneven brown pencil mark. These lesions covered an area about 2 cm. in diameter. There were no symptoms or inflammatory reactions in any of the patients. All 3 were concerned about only the appearance of the lesions.

By scraping with firm pressure a scale or piece of the keratin layer could be removed, which showed a large number of hyphae on microscopic examination with a 10 per cent solution of potassium hydroxide. The mycelial threads were greenish brown in color and had a smooth wirelike appearance compared with those seen in infection with Trichophyton purpureum. Culture on Sabouraud's mediums developed a slow-growing black colony, which later formed a raised furry center. The organism was identified as Cladosporium wernecki,[2] the same that was observed by the Brazilian investigators.

In the 1 patient who was followed, the lesion disappeared after a few applications of an ointment with 3 per cent sulfur and 2 per cent salicylic acid and did not reappear.

SUMMARY

Tinea nigra (black fungus) of the palm of 3 white North Americans stationed in the Panama Canal Zone is reported. The disease is caused by a black fungus, Cladosporium wernecki, is symptomless and is of only cosmetic importance.

2. Conant, N. F.: Personal communication to the author.

TOPICAL PENICILLIN THERAPY

III. Hemin Penicillin Ointments

A. J. LIEBMANN, Ph.D.; LEON GOLDMAN, M.D.;
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CINCINNATI

Penicillin ointment mixtures have been observed to be effective in the treatment of certain local cutaneous infections.[1] However, topical therapy with penicillin is

This work was aided in part by a grant from Schenley Laboratories, Inc.

From the Schenley Research Institute and the Department of Dermatology and Syphilology of the College of Medicine of the University of Cincinnati.

1. Goldman, L.; Suskind, R. B., and Friend, F.: Studies in Topical Penicillin Therapy: II. The Principles of Local Therapy with Penicillin Ointment Mixtures, Arch. Dermat. & Syph. **55**:793 (June) 1947.

not so simple as it first would appear, since many factors affect such forms of penicillin therapy. In previous reports [2] the excellent sensitizing qualities of the penicillin per se or the penicillin mixture, the stability of the mixture and the diffusion of penicillin through the mixture were considered as some of the factors affecting treatment. In this report we should like to mention our initial experiences with the effect of the addition of an active therapeutic agent to the penicillin ointment mixture. Certain obvious qualifications are necessary for the consideration of additional therapeutic, as opposed to vehicular, agents to penicillin ointment mixtures. First, the substance should not inactivate penicillin. Second, the substance should increase the therapeutic quality of the ointment by extending the range of "antiseptic" quality of the ointment mixture, for example, penicillin-streptomycin mixtures or penicillin plus compatible antiseptics. The therapeutic quality may also be enhanced by the addition of agents having properties other than those of bactericidal activity or of bacteriostasis. Penicillin ointments have no tissue growth activity. In fact, strong penicillin mixtures are supposed to interfere with normal tissue growth in wound repair. So far, this has not been our experience [2b] with concentrations of 20,000 units of penicillin per gram of ointment base. To satisfy the theoretic and actual clinical inadequacies of pure penicillin ointment the addition of hemin to the penicilln mixture was suggested. Hemin is a crystalline iron compound, $C_{34}H_{32}N_4O_4FeCl$. Its preparation and properties will be described in a subsequent report.[3]

Preliminary studies of the stability of various penicillin ointment combinations indicate that the hemin-penicillin mixtures may be more stable than ordinary penicillin mixtures.

The cases in which hemin-penicillin ointments have been used in more than a year may be divided into three general groups:

Group I: Ulcer syndromes
Group II: Postoperative wounds
Group III: Miscellaneous

Because of the high sensitizing qualities of penicillin ointment treatment with penicillin ointment mixtures has been limited to areas of the body other than the face. In any study of the factors influencing the healing of ulcers many different aspects must be considered; otherwise evaluation is not critically sound. Most of our experience with ulcers has been in the difficult groups of ulcers as part of far advanced stasis syndromes. Hemin-penicillin mixtures are tolerated here better than penicillin mixtures. In previous work with the treatment of stasis syndrome the irritating effect of heavy greasy ointments has been noted. Hemin-penicillin mixtures were definitely more effective than plain hemin salves (1 per cent) in the few instances in which hemin was used. From our experience also, hemin-penicillin mixtures were superior to red cell salves. It is our impression, without any sound critical data, that hemin-penicillin mixtures were superior to penicillin mixtures containing the same concentration of penicillin. In some instances, when application of hemin-penicillin mixtures was used as part of the routine treatment with bed rest and leg elevation, an effort was made to determine first whether simple

2. (*a*) Goldman, Suskind and Friend.[1] (*b*) Goldman, L.; Friend, F., and Mason, L. M.: Dermatitis from Penicillin with Special Reference to the Development of Eczematous Hypersensitivity, J. A. M. A. **131**:883 (July 13) 1946.

3. Liebmann, A. J.: Unpublished data.

rest and elevation were effective before the hemin-penicillin was used. Even in far advanced stasis syndrome, stages III and IV of our classification,[4] with eczematoid reaction, hemin-penicillin was of definite value. In a few instances in which penicillin had been used on one ulcer and hemin-penicillin on a similar type of lesion on the same leg, the hemin-penicillin mixture was more effective. Similar results were obtained in only 2 instances in which this comparison had been made on ulcers on opposite legs. In ambulatory patients hemin-penicillin mixtures were combined with pressure type dressings. In our series of twenty-five ulcer areas no local or systemic reactions were produced by the hemin-penicillin mixture.

In 32 cases hemin-penicillin applications were used as routine dressings after biopsy, excision of cutaneous malignant growths and nevi and after electrosurgical treatment of papillomas. In areas of excision the hemin-penicillin was spread into the wound just before suture and also over the incision line and then covered by sterile gauze with petrolatum. In only 1 of the patients was there a small stitch abscess. After electrosurgical treatment the lesions were curetted, and then hemin-penicillin was packed over the areas and bandaged. Daily applications were continued until healing occurred. In no instance were comparative experiments made with penicillin mixtures alone without the hemin. In some experiments with animals [3] there were indications of better wound healing with hemin-penicillin ointment than with penicillin ointment or chlorophyll ointment.

Patients with impetigo, ecthyma and infectious eczematoid dermatitis were also treated with hemin-penicillin mixtures, and the results were comparable with those in studies in which we had used penicillin ointment alone. As far as we could determine, the addition of hemin was of no special value in those instances. No contact dermatitis resulted from the use of the penicillin mixture.

In only 1 case did the patient show evidence of reaction to the mixture. This case has been mentioned before in a review [2b] of reactions to penicillin in topical therapy. Generalized urticaria followed after five days of continued application of hemin-penicillin ointment to the skin after extensive electrosurgical removal of nevi. Reactions in tests with penicillin were negative. No tests were made with hemin. There is not sufficient data at present to indicate that the addition of hemin affects the sensitizing quality of penicillin.

CONCLUSIONS

In an attempt to increase the therapeutic efficiency of penicillin ointments, 1 per cent hemin was added to a standard penicillin ointment. Hemin was added to provide factors of so-called tissue growth in addition to bacterial and bacteriostatic qualities of the penicillin. The addition of hemin did not affect the stability of the penicillin; in fact, it seemed to increase it. In a small series of patients hemin-penicillin mixtures were effective in local treatment of chronic resistant ulcers and in postoperative wound healing. It was felt that the hemin-penicillin mixture was more effective than penicillin alone. In cases of superficial cutaneous infections, hemin-penicillin possessed no advantages over penicillin ointments of similar concentrations. In only 1 instance in the series was there any reaction associated with the local use of hemin-penicillin. This was of urticaria, the causation of which was not proved. Further clinical trials and laboratory investigative studies with hemin-penicillin or hemin plus a less sensitizing antibiotic agent are indicated.

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4. Goldman, L., and Corrill, E. M.: Studies in Some Capillary Fragility States in Dermatology, J. Invest. Dermat. **6**:129 (April) 1945.

BULLOUS ERUPTION RESEMBLING DERMATITIS HERPETIFORMIS, ASSOCIATED WITH FOCAL INFECTION

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AND
WARREN L. MACAULAY, M.D.
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In a previous communication,[1] one of us (S. E.) reported 2 cases of localized bullous eruption associated with focal infection, which cleared up promptly after the removal of abscessed teeth. The following case apparently belongs to the same group; yet it differs in that the patient suffered from a generalized eruption which clinically and histologically was indistinguishable from dermatitis herpetiformis.

REPORT OF A CASE

History.—Mrs. F. T., 69 years of age, was first seen at the clinic on Aug. 19, 1946, with an eruption of red scaly lesions which covered the hands, arms, legs and other parts of the body. The dermatosis had originated about three to four weeks previously on the lateral aspect of the left leg and soon involved the other areas. The eruption itched and burned at times, mostly during the day.

About a year prior to this the patient had suffered from dermatitis, allegedly from a begonia plant. Some pigmented areas of the skin were still noticeable.

The patient did not feel well otherwise and complained vaguely of "stomach trouble."

On examination a generalized papular eruption was observed. The forearms and the dorsa of the hands were chiefly involved. The individual lesions consisted of violaceous flat-topped sometimes umbilicated papular and annular lesions. The eruption resembled lichen planus. However, there were numerous excoriations and scratch marks, an observation not commonly seen in lichen planus. At this time no blisters were present. A tentative diagnosis of atypical lichen planus was made. The patient was treated with 3 per cent coal tar solution (liquor carbonis detergens) in petrolatum and vitamin B complex by mouth. The eruption did not improve. About two weeks later the patient discovered the first blister near the site of the original lesion on the lateral aspect of the left leg. After that blisters appeared on both legs and arms. The patient was admitted to the hospital on September 7. The history revealed that she had taken various drugs, among them phenolphthalein. In fact, she secretly continued to take some proprietary laxatives containing phenolphthalein for a few days in the hospital.

Examination.—The patient appeared ill. There was a diffuse eruption of pustules and large bullae. Many of the latter arose from apparently normal skin. There were also numerous crusted and scaly lesions of various sizes. Many of these appeared on a reddened infiltrated base and presented polycyclic outlines. The eruption was located essentially on the face, upper part of the chest and back, hips, arms and legs. The location and clinical picture were suggestive of dermatitis herpetiformis, a resemblance which became more apparent during the course

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From St. Joseph's Hospital and the Marshfield Clinic.

1. Epstein, S.: Persisting Localized Bullous Eruption of the Skin Associated with Focal Infection, Arch. Dermat. & Syph. **56**:452 (Oct.) 1947.

of the disease, as demonstrated by the accompanying photograph (fig. 1). Itching and burning were present at times. The Nikolsky sign was not present; patch tests with 25 per cent potassium iodide did not produce any reaction either on normal or on previously diseased skin. The biopsy report of a bulla was as follows (Dr. Felix Pinkus):

Below and within the epidermis were varying degrees of a heavy exudation. The surrounding epidermis, although rather thick, was normal and showed a thin horny layer, a thin keratohyaline layer and almost regular rete pegs and papillae. The papillary layer showed a moderately dense round cell infiltration, especially around the blood vessels.

Fig. 1.—Clinical appearance of the dermatitis herpetiformis-like eruption before extraction of the teeth.

In the center of the field a heavy exudation gave rise to a large blister. At the border there was spongiosis, with more serous exudation than cellular transmigration. Approaching the center the spongiosis progressed to formation of small vesicles. As the vesicles increased in size they displaced the epidermis, until all the epithelium at the lower side was gone. In this stage the vesicle was capped by stretched epithelium above and embedded in an inflamed and necrotic papillary body below (fig. 2). These vesicles were filled with coagulated serum and numerous uninuclear and polymorphonuclear cells, including many eosinophils. In another section a large undivided blister was seen; the large amount of fluid present, in

contrast with the small concentration of cells, showed that the exudative process was a rapid one. The roof of this blister showed thin stretched epidermis, with remnant shreds of rete pegs still attached. The bottom of this blister presented a cup-shaped thick necrotic layer. Below this bullous formation was a moderate round cell infiltration, which was limited to the widened and edematous papillary body.

Dr. Pinkus suggested a diagnosis of dermatitis herpetiformis, if toxic dermatitis from phenolphthalein could be excluded.

Intradermal tests with various bacterial vaccines were carried out twice, with negative results. The tests were performed with stock vaccines of staphylococci, streptococci, pneumococci and Escherichia coli.

Fig. 2.—Histologic section (low power) of moderately sized blisters.

The results of the general examination were essentially negative except for a poor condition of her teeth. The report of the roentgenologic examination was as follows (Dr. J. M. Wickham): "Roentgenograms of the remaining teeth showed many of the upper teeth to be devitalized. The right upper first bicuspid and the left upper lateral incisor showed considerable destruction and cavitation of their crowns. The right upper bicuspids showed an increased prominence of the peridental membrane and an abscess at the tip of the root of the first. Considerable retraction and erosion of the alveolar margin was present in the lower incisor, cuspid and bicuspid areas as well as between the right upper first and second molars and the left upper molars." The blood cell count was essentially normal except for mild secondary anemia. Eosinophils were absent on admission, but later

ranged between 2 and 20 per cent. The white blood cell count varied between 8,000 and 20,000. The sedimentation rate on admission was 15 mm. per hour.

Diagnosis.—The following diseases were considered: dermatitis herpetiformis, pemphigus vulgaris, bullous eruption due to drugs and bullous eruption associated with focal infection.

Clinical Course.—In spite of discontinuation of all drugs, new bullae continued to appear. The resemblance to dermatitis herpetiformis became more apparent. Methylrosaniline chloride and soothing lotions were applied locally. General treatment consisted of injections of crude extract of liver, vitamins and intravenous fluids as indicated. "Pyribenzamine hydrochloride" N. N. R. (tripelennamine hydrochloride) was given without effect and therefore discontinued. On September 30 sore throat with a white exudate developed. One unit of plasma was given intravenously on October 3, as replacement therapy. Treatment with sulfadiazine and sulfathiazole was started then, but discontinued after two doses because nausea developed and the patient refused further treatment. On October 15 treatment with sulfapyridine was started in doses of 1 Gm. three times a day. This also had to be discontinued the next day on account of gastrointestinal upset. The eruption grew worse and almost covered the whole body. Numerous new and larger bullae appeared. At this time an etiologic relationship between the infected teeth and the bullous eruption was seriously considered. On October 19 the maxillary left lateral incisor and the maxillary right cuspid were removed. A granuloma was observed on the latter. Cultures of the teeth revealed Streptococcus hemolyticus, Staphylococcus aureus, Staphylococcus albus, Pneumococcus and Hemophilus influenzae.

Up to this time the patient had always refused penicillin injections. Her objections were finally overcome, and penicillin therapy was instituted the day before the extractions. Twenty-five thousand units were given five times a day. Improvement was noticeable after a few days. New blisters continued to appear, but at a much slower rate. Penicillin therapy was discontinued on October 31, after twelve days. At that time the patient had improved greatly; still new blisters appeared. A week later the eruption again grew worse; more new bullae developed and the itching and burning returned. Therefore, four more teeth were removed on November 20, among them the maxillary right first bicuspid, which showed a definite root abscess. Cultures of these teeth revealed the following micro-organisms: Neisseria organisms, pneumococcus, Staphylococcus albus and an unidentified gram-negative coccobacillus (bacteroid).

On account of the patient's objection to penicillin and the relatively good general condition, penicillin was not given this time.

Following the extraction, there was improvement in the condition of the skin. From the third day on, no new bullae appeared, and six days after the removal of the teeth, only pigmentation and a few scattered crusted lesions persisted. The latter healed within two more days, and the skin remained well thereafter.

On November 29, nine days after the last extraction, the patient felt nauseated and vomited and complained about pain in the upper right quadrant of the abdomen. Examination revealed dulness in the right upper quadrant, extending about 3 fingers below the costal margin. There was moderate tenderness over this area. During the following day a moderate degree of icterus developed. The internists favored the diagnosis of acute infectious hepatitis, perhaps due to the injection of plasma. The incubation period in infectious hepatitis [2] is sixty to one hundred and twenty days for virus B. The possibility of an obstructive

2. Alvarez, W. C.: Therapeutic "Information Please": Gastroenterology, J. A. M. A. **132**:970 (Dec. 21) 1946.

disease of the gallbladder could not be excluded. Penicillin therapy was resumed, 25,000 units every four hours. The patient had always shown a low grade fever. The temperature, which had varied between 97 and 100.8 F., now rose to 102 F. The patient appeared seriously ill. A roentgenogram of the abdomen revealed a calculus in the right upper quadrant, but the roentgenologist was unable to determine whether it belonged to the kidney or gallbladder. Surgical consultation was secured. Roentgenologic examination of the gallbladder and intestinal tract was postponed because of the patient's poor condition. The skin at that time was normal except for residual pigmentation. There was no itching. On December 14, at 12:15 a. m., apparently a cerebral accident occurred. The attack began with a loud cry followed by convulsions of the right side. The mouth was pulled to the right, and the eyes deviated to the left. Respiration was deep and labored. The patient remained unconscious for several hours; although she subsequently recovered somewhat from this attack, her general condition now took a downward course. She had difficulty retaining any food. On December 20, the patient regained partial control of all extremities and she was able to eat a few foods. However, she grew steadily worse and weaker and died on December 23.

Permission for an autopsy was denied.

COMMENT

This case appears interesting from an etiologic angle. The clinical and histologic picture and the eosinophilia are fully compatible with a diagnosis of dermatitis herpetiformis. The lichen planus-like dermatosis that preceded the bullous eruption might have been a precursor. It is known[3] that the typical herpetiform eruption of Duhring's disease may be preceded by noncharacteristic manifestations. However, the dramatic response to the elimination of the foci of infection suggests that this case belongs to the group of bullous eruptions associated with focal infection. The sequence of events was as follows:

1. The patient's bullous eruption grew worse in spite of local treatment and supportive measures.

2. The removal of two infected teeth combined with penicillin therapy led to definite improvement, but bullae still appeared.

3. Deterioration and return of the generalized eruption followed the cessation of the penicillin therapy.

4. The removal of four additional teeth, among them one which roentgenologically showed a definite abscess, was followed by a rapid recovery of the skin.

The previous report of 2 cases,[1] however, concerned localized bullous eruptions, whereas this report deals with a generalized bullous eruption resembling much more dermatitis herpetiformis. The latter disease originates only rarely in old age.[3] But the advanced age of the patient and the observation that the first bullae occurred at the site where the preceding dermatosis originated form a parallel to the cases of bullous eruption associated with focal infection previously described.[1] For these reasons, we are inclined to consider the dermatitis herpetiformis-like eruption in our patient, also, a bullous eruption associated with focal infection. The relationship between this eruption and true dermatitis herpetiformis has been discussed briefly before.[1] The role of bacterial allergy in some cases of Duhring's disease is recognized. There may be a common denominator for the two diseases. However, further observations and studies are necessary.

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3. Riecke, E.: Dermatitis herpetiformis, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1932, vol. 7, pt. 2, p. 549.

We realize that the concluions drawn from this case are debatable, inasmuch as death supervened after an observation period of only one month and because of the hepatic changes. No matter what the cause of her hepatitis may have been, the possibility remains that this may have played a part in her eruption. Nonetheless, focal infection appears to have been the outstanding factor of this bullous eruption. It is our purpose to point out this relationship.

SUMMARY

A case of a generalized bullous eruption is reported, in which the favorable response to the removal of foci of infection strongly suggests an etiologic relationship. Clinically the case presented the picture of bullous dermatitis herpetiformis.

CONSTRICTION OF THE FINGER SIMULATING AINHUM

Report of a Congenital Case

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A case of congenital anomaly simulating ainhum of the little finger is reported, because a search of the available literature failed to disclose any similar report.

True ainhum is usually encountered as a tropical or semitropical disease of great chronicity. It usually occurs in the Negro and is confined, with rare exceptions, to the male. Ainhum is characterized by spontaneous amputation of the toe, usually the fifth toe and in some cases the fourth toe. The amputation is the result of a constricting band or line of demarcation which gradually forms at the proximal interphalangeal joint of the fifth toe and gradually deepens its furrows until there is spontaneous amputation.

All cases of digital amputation are not true ainhum. Ainhum-like constrictions of the digits occasionally occur as symptoms of, or associated with, an underlying constitutional disease. The two types, true ainhum and ainhum-like syndrome, should be distinguished from one another. The ainhum-like syndrome has been reported as a manifestation of, or associated with, leprosy,[1] scleroderma, trophoneurosis,[3] syphilis,[4] metabolic diseases,[4] cicatrix,[5] hyperkeratosis palmaris et plantaris,[6] pityriasis rubra pilaris,[7] syringomyelia[8] and a form of congenital anomaly.

From the Department of Dermatology, Northwestern University Medical School, Dr Edward A. Oliver, Chairman.

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2. Footnote 2 deleted.

3. Matas, R.: The Surgical Peculiarities of the American Negro: A Statistical Inquiry Based Upon the Records of the Charity Hospital of New Orleans, La., Decennium 1884-1894, Philadelphia, P. Dorman, 1896, p. 123.

4. Butler, H. W.: Ainhum (Doctylolysis Spontanea), M. Clin. North America **9**:1187 (Jan.) 1936.

5. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939, p. 587.

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(Footnote continued on next page)

REPORT OF A CASE

R. G., a 9 year old white girl, was seen with an abnormality of the right hand, which had been present since birth. The thumb and the middle and ring fingers of the right hand were normal in size and shape. The index finger was smaller and of greater thickness than the corresponding finger of the left hand. The little finger was normal in size, but there was a narrow linear constricting band in the skin just proximal to the first interphalangeal joint (figure). The clinical picture was like that of ainhum. There was no limitation of motion. Pain and tenderness were absent.

Physical examination showed normalcy in every respect except for convergent strabismus. The reaction in the serologic test of the blood (Kahn) was negative.

Roentgenologic examination of the right hand revealed a shortening of the second and digital phalanges of the index finger, causing the finger to be much smaller than the corresponding finger of the left hand. Examination of the little finger of the right hand disclosed no bony changes. There was a constriction of the soft tissues about the center of the middle phalanx. The left hand was normal.

Ainhum-like constriction of the little finger.

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7. Stelwagon, H. W.: Treatise on Diseases of the Skin for the Use of Advanced Students and Practitioners, ed. 7, Philadelphia, W. B. Saunders Company, 1914, p. 626.

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SUMMARY

A rare case of a congenital anomaly simulating ainhum is reported. It occurred in a young white girl and involved the little finger of the right hand.

Ainhum-like constrictions have been reported as a manifestation of, or associated with, leprosy, scleroderma, syphilis, metabolic diseases, cicatrices, trophoneurosis, hyperkeratosis palmaris et plantaris, pityriasis rubra pilaris, syringomyelia and a form of congenital anomaly.

30 North Michigan Avenue.

FAILURE OF 2,3-DIMERCAPTOPROPANOL (BAL) IN TREATMENT OF ARGYRIA

THEODORE ROSENTHAL, M.D.
AND
ARTHUR OLLSWANG, M.D.
NEW YORK

Argyria is a disfiguring cosmetic disease for which no completely successful treatment has as yet been developed. Stillians and Lawless [1] described a method in which a mixture of potassium ferricyanide with sodium thiosulfate was injected intradermally. They stated the belief that a large part of the silver could be removed from the skin in this manner. Andrews [2] employed this method "with questionable benefit" and reported 2 cases in which the passage of time seemed the most important therapeutic consideration. Stillians,[3] in a later paper, provided a thorough review of the literature on argyria.

The recent reports in the medical literature on the value of BAL (2,3-dimercaptopropanol) [4] in certain types of metallic intoxication prompted the use of this substance in an attempt to help a patient with generalized argyria. These papers have been on the value of BAL in the treatment of arsenical and mercurial poisoning and also intoxication following the injection of gold salts. Little is known at the present time of the effect of BAL in the treatment of poisoning by other heavy metals.

Olcott and Riker [5] reported recently on the use of BAL in animals in whom silver salts had been deposited experimentally. Their conclusions are of interest: "It appears from these observations on a limited number of animals that BAL is incapable of mobilizing silver, which is deposited in the tissues as metallic silver or silver oxide."

From the Bureau of Social Hygiene, Department of Health.

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4. Sulzberger, M. B., and Baer, R. L.: Development and Use of BAL, J. A. M. A. **133**:293 (Feb. 1) 1947. Eagle, H.: The Systemic Treatment of Arsenic Poisoning with BAL (2,3-Dimercaptopropanol), J. Ven. Dis. Inform. **27**:114 (May) 1946.

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REPORT OF A CASE

Mrs. A. R., 46 years old, was seen in November 1946, at which time she presented a bluish gray uniform coloration of the face, neck, shoulders, hands and conjunctivas.

The patient stated that six years previously, in 1940, she had used a 10 per cent solution of "argyrol" (mild protein silver), instilled in her nose three times a day, for infected nasal sinuses for a period of nine months. Several months after terminating the treatment with "argyrol" she and her friends noted a beginning pigmentation of the face and conjunctivas.

A number of dermatologists saw her at that time, and all made a diagnosis of argyria. About two years prior to our contact a physician gave her several treatments with ultraviolet rays, which were followed by an intensification of the pigmentation. Her previous medical and surgical history was irrelevant.

Physical examination revealed a diffuse bluish gray discoloration of the face, neck, shoulders, hands and conjunctivas. Colored photographs were taken before treatment to serve as a basis for comparison with the future appearance of the skin. A portion of the skin was removed for histologic examination. Treatment was begun November 8 with the injection of 1 cc. of a 10 per cent solution of BAL intramuscularly twice a day for ten days. Daily injections were then given at intervals until March 31, 1947, at which time the patient had received a total of seventy-six injections, amounting to 132 cc. Several times in the course of treatment injections had to be discontinued for several days, because the patient complained of severe abdominal cramps and pains. These would usually disappear after several days, at which time treatment was resumed.

At the end of this time there was no change in the skin apparent to the eyes of several dermatologists, although there was an interesting psychic phenomenon evidenced by the fact that the patient insisted that there was improvement. Stillians observed a similar phenomenon in a patient. He used a card painted to match the color of the skin as a control. A number of colored photographs taken in the course of the patient's treatment did not reveal any change in the appearance of the patient's skin or conjunctivas.

Several months after the injections had been discontinued and it was obvious that no change had occurred, a trial with BAL ointment was attempted. A pea-sized quantity of 5 per cent BAL ointment in a "carbowax" base (furnished by the Army Chemical Center) was rubbed into the right temporal region daily for thirty days. Definite dermatitis was produced in this manner, with no change whatever in the color of the skin.

Laboratory Observations.—Specimens of urine were examined daily for the first ten days following injection therapy and thereafter at frequent intervals. No abnormalities indicating renal irritation were noted.

Specimens of urine were examined during this period for the presence of silver by a special technic [6]; no silver was detected in the urine at any time.

Determinations of blood pressure were made every second day during treatment; no changes were encountered.

A small section of skin was removed for histologic examination. The report of the pathologist [7] was as follows: "Under high magnification there could be observed

6. Umberger, C. J.: Personal communication to the authors.

7. Ginzler, A. M.: Personal communication to the authors.

a deposition of fine black granules in the subepidermal layer of the corium. With dark field illumination these granules were refractile. There were no other significant histologic changes."

SUMMARY AND CONCLUSION

A patient with decided generalized argyria of six years' duration was treated with BAL (2,3-dimercaptopropanol) both by intramuscular injection and by topical application. Treatment failed to effect any improvement in the cutaneous or conjunctival discoloration, colored photographs at intervals being utilized as a gage of progress.

There was no evidence of toxicity from the use of BAL other than the production of dermatitis when the ointment was applied repeatedly to the same area of skin.

The experience in this case would seem to bear out the conclusions of Olcott and Riker, based on studies of animals: "It seems likely . . . that BAL should prove of little or no value in the treatment of argyria. . . ."

1 West Ninety-First Street.

601 West End Avenue.

News and Comment

GENERAL NEWS

Medical Records of Army Personnel Treated for Syphilis Available to Physicians.—The Veterans Administration has issued the following announcement:

"The Veterans Administration has in its custody the majority of syphilis records of those Army personnel who were treated for this disease while in active service, and in many instances can procure informative data from the syphilis records of other than Army personnel. It is thought that many physicians treating veterans for syphilis as private patients would find a résumé of the syphilis record useful since the details of treatment, results of spinal fluid examinations and blood serologies are incorporated in the records.

Résumés of these records are available to physicians who are treating such veterans provided authorization for the release of the data is given by the veteran. Requests for the résumés accompanied by an authorization for the release of the data, dated and signed by the veteran, should be addressed to the Dermatology and Syphilology Section, Veterans Administration, Munitions Building, Washington 25, D. C. It is most important that the veteran's Service Serial Number and other identifying information, such as the date of enlistment, the date of discharge, rank and organization, be included.

Ordinarily, the résumés can be furnished in approximately two weeks from the date of the receipt of the request and signed authorization."

Silver Medal Award.—At the Annual Session of the American Medical Association at Chicago, June 1948, the Silver Medal in group II was given to Dr. J. Walter Wilson, University of Southern California and Dr. Orda A. Plunkett, University of California, Los Angeles, for the exhibit on Practical Medical Mycology, "Culture and Identification of Fungi as an Office Procedure."

An exhibit of Dr. Helen Ollendorff Curth, Columbia University, College of Physicians and Surgeons, New York, on "Cancer and Acanthosis Nigricans" received Honorable Mention in group I. This is the same exhibit which was given first prize at the December 1947 meeting of the American Academy of Dermatology and Syphilology in Chicago.

Medical Journals for Devastated Countries.—Requests from libraries, medical societies and individual physicians in various devastated countries are being received almost daily. If physicians have extra copies of medical journals or copies for which they have no further use, it will be greatly appreciated if they will send them to the headquarters of the Association for distribution abroad.

New Periodical.—The first issue of volume 1 of a new periodical on etiology and treatment, published in France, has recently been issued. The periodical is *Syntheses of Semiology and Therapeutics.* The publication office is 40 Boulevard Suchet, Paris 16a. The price of the periodical is 85 francs.

Society Transactions

CHICAGO DERMATOLOGICAL SOCIETY

Marcus R. Caro, M.D., *President*

Leonard F. Weber, M.D., *Secretary*

Feb. 20, 1946

Urticaria Pigmentosa. Presented by DR. S. ROTHMAN and (by invitation) DR. Z. FELSHER.

Lupus Erythematosus Limited to the Scalp. Presented by DR. PAUL R. GRIFFITH (by invitation).

Mrs. D., a white woman aged 71, suffered a burn from a permanent wave machine in the middle portion of the frontal area of the scalp in 1928. A scar the size of a five cent piece resulted and has been devoid of hair ever since.

In January 1944 redness appeared on the frontal part of the scalp, and shortly thereafter the hair in the same area began falling out. The patient stated that her scalp was asymptomatic then and has remained so ever since, but it would become redder for four or five days after each time her hair was shampooed and set.

In April 1945 she consulted a physician for the first time, and during the subsequent three weeks she received eight treatments with ultraviolet rays on the scalp, some of the treatments being with a cold quartz pencil. After these treatments the redness seemed to lessen, but the scalp became drier and scalier.

No history can be elicited as to the presence of lesions elsewhere on the body except for the hypothenar erythematous vascular ones which have been present all her life.

The patient was first seen by me in January 1946, at which time the major part of the frontal aspect of the scalp was involved with erythema, which was circumscribed but not sharply demarcated, almost complete alopecia, some thin scaling, atrophy and follicular dilatation. The erythema has lessened considerably following the use of aluminum subacetate wet dressings. The Kahn reaction of the blood was negative in January.

A biopsy performed on February 2 showed a thin non-nucleated scale, loosely attached to a flat atrophic epidermis. The granular layer was discontinuous, in parts there was intracellular edema of the epidermal cells, and there was liquefaction degeneration of the basal layer. In most of the specimen there was a densely packed cellular infiltrate in the upper part of the corium that hugged the epidermis. This was composed largely of lymphocytes. Within the upper part of the corium the blood vessels were distended. A densely packed zone of infiltrate was present about the hair follicle. The elastic fibers were destroyed throughout the entire infiltrated area.

Gold compound therapy has been withheld in view of the patient's hypertension of 180 to 220 systolic and 90 diastolic and moderate albuminuria. The toxicity, if any, of her thyroid adenoma has not as yet been determined. Since February 12, she has been taking a capsule containing 1 grain (0.065 Gm.) of iodoform and 4 grains (0.26 Gm.) of ferrous sulfate three times a day.

DISCUSSION

DR. OLIVER S. ORMSBY: I think that the diagnosis is correct. It is not uncommon to see lupus erythematosus limited to the scalp. It always leaves an atrophic area on which the hair does not return. It can be improved with treatment.

DR. CARL W. LAYMON, Minneapolis: In cases of patchy baldness with scarring, there are three main diagnostic possibilities: pseudopelade, folliculitis decalvans and lupus erythematosus. One of the foremost features of pseudopelade is the complete absence of inflammatory changes, while in folliculitis decalvans there are follicular pustules at the borders of the plaques. In some cases of long duration the folliculitis may not be present, making it almost impossible to differentiate the disease from pseudopelade. In my opinion the diagnosis in this case is correct as presented.

DR. MARCUS R. CARO: I should like to hear suggestions for treatment. Because of the hypertension present in this patient, gold compound therapy was not seriously considered.

DR. HERBERT RATTNER: I think that in view of her advanced age, it would be sufficient in this case to treat the lesions by light pressure with solid carbon dioxide.

DR. FREDERICK R. SCHMIDT: As to the use of gold compound in lupus erythematosus, I have not observed any contraindication as far as high blood pressure is concerned. I have 4 patients with hypertension now who are receiving colloidal gold compound. The blood pressure in these patients has not been altered in any way by treatment with gold compound. I think that it is safe to give colloidal gold compound, because it does not have the same biologic action as crystalloidal gold compound. I am using 5 cc. of a preparation containing 17.2 mg. in each cubic centimeter.

Arthropathic Psoriasis. Presented by DR. FRANCIS E. SENEAR and (by invitation) DR. PAUL R. GRIFFITH.

A 30 year old white man, a patient in the Illinois Research and Educational Hospital, was seen in consultation by the department of dermatology. There was a history of stiffness and pain in the knees, ankles, wrists and fingers, occurring episodically for the past fourteen years. For five months cutaneous lesions had been present on the tips of the fingers, toes and extensor surfaces of the elbows.

Roentgenograms showed skeletal changes consistent with a diagnosis of rheumatoid arthritis. The results of other laboratory studies were noncontributory.

There were erythematous areas with rupioid hyperkeratotic scale on the extensor surfaces of the elbows. Similar lesions had been present on the extensor surfaces of the knees and forearms. The distal portion of the terminal phalanges of the fingers and toes were capped by thick yellow scale, completely surrounding the finger tips and lifting the nails from their beds. Pitting and yellowish discoloration of the nails were present.

Histologic examination showed a thick parakeratotic scale. The epidermis showed acanthosis and considerable elongation of the rete pegs to a uniform depth and fusion of many pegs. The granular layer was discontinuous, and the suprapapillary rete was thin. The papillae were elongated and vascular, and in places there was dilatation of the lymphatic vessels. The papillae contained a dense infiltrate of lymphocytes and a few polymorphonuclear leukocytes, and this infiltrate was present about the superficial blood vessels. Some of the cells invaded the epidermis and were present within the scale.

DISCUSSION

DR. ARTHUR W. STILLIANS: It is unusual in my experience to see arthritis precede psoriasis for such a long time and to see a case with a mild outbreak with such acute psoriasis lesions only on the digits. I think that it illustrates the value of mild treatment in acute outbreaks. The man has improved on what Dr. Senear called "studied neglect." He received a great deal of vitamins and rest.

DR. RUBEN NOMLAND, Iowa City: I belong to the group that thinks that arthropathic psoriasis is a special type of arthritis occurring with psoriasis. I think that one should watch for the occurrence of acute arthritis with acute psoriasis which may be Reiter's disease. It may look like gonorrheal arthritis with gonorrheal parakeratosis, or it may be like acute arthritis with pustular psoriasis-like lesions of the skin. The symptoms of Reiter's disease may include acute arthritis, conjunctivitis, nongonorrheal urethritis and an eruption resembling either pustular psoriasis or gonorrheal parakeratosis.

DR. HERBERT RATTNER: A few years ago Dr. Oppenheim recommended the use of sodium iodide for a patient with similar disease in County Hospital. There was a good, though temporary, response to the drug in that case and I wonder whether Dr. Oppenheim would tell us the rationale and why he favored the sodium salt.

DR. MAURICE OPPENHEIM (by invitation): I have treated a number of patients with arthropathic psoriasis with high doses of sodium iodide, with good results. I believe that that is the only drug which shows results. I prescribe 10.0 sodium or potassium iodide to 180.0 distilled water and start with 3 tablespoons in milk after each meal and increase gradually to 6 and 8 tablespoons, that is about 3 to 8 Gm. daily. There is no doubt that the arthropathic form of psoriasis is a special form of this disease. Dr. Cohen and I treated a patient, who was presented at the conference of the Mount Sinai Hospital, with erythroderma psoriaticum and a high degree of arthritis deformans, with good result. I would like to recommend this treatment as being superior to treatment with salicylates and all other drugs. The pain in the joints subsides after the iodide therapy, but the disease in all these cases is inclined to recur.

DR. L. F. WEBER: I was glad to hear Dr. Nomland speak about Reiter's disease. There are several points against that disease in this case. This patient has never had a urethral discharge. In those cases that are reported of Reiter's disease the patients have had genital and ocular manifestations. It is interesting to hear the discussion about the treatment. It seems to me that often the patient who has had no treatment makes remarkable improvement.

DR. FRANCIS E. SENEAR: I am sorry that the cutaneous lesions of this patient have done so well with "studied neglect," because when we saw him last week he had cutaneous horns on both sides of the wrist, where only erythematous patches showed today. The soles had the appearance of a bas relief map. He had the picture of severe keratosis, the type seen in keratosis blennorrhagica. This man is on the medical service, where his arthritis will be treated and his psoriasis will probably follow the same course, as both the arthritis and the psoriasis have improved rapidly.

Pulsating Angiomas Associated with Hepatic Disease. Presented by DR. FRANCIS E. SENEAR and (by invitation) DR. M. J. BRUNNER.

This is the case of a 45 year old bartender, a patient in the Illinois Research and Educational Hospital, who was seen in consultation by the department of dermatology.

For some twenty-five years he had taken four or five glasses of beer and four "shots" of whisky daily. One month before admission an eruption developed on the face and neck. Two weeks later, progressive swelling of the legs and abdomen developed and yellow staining of the skin and scleras was noted.

The physical examination showed mild jaundice, ascites and edema of the legs. The liver and spleen were not palpable. There was moderate anemia, and blood protein determination showed the albumin-globulin ratio to be 2.3 to 4.7. A test of hepatic function with sulfobromophthalein indicated a moderate degree of hepatic damage.

The dermatologic examination revealed bright red-purple papules on the face, neck, chest and arms (including the palms). These papules consisted of three elements: a central pulsatile blue-red elevation, surrounding radiating telangiectasia and erythema. Point pressure on the central elevation caused complete blanching of the lesions. There was a slight mottled erythema of the thenar and hypothenar eminences of the palms.

During the period of hospitalization, new arterial spiders appeared and old ones regressed. Progressive improvement was noted in the hepatitis.

DISCUSSION

DR. HENRY E. MICHELSON, Minneapolis: The association of these small angiomas with hepatic disease is well known. Such lesions have been seen to occur in patients who are undergoing malarial treatment for syphilis, in whom there was some hepatic damage from the malaria.

DR. THEODORE CORNBLEET: Perhaps some of the new approaches in the consideration of cirrhosis of the liver may be of value here. The sulfur-containing amino acids are thought to be of value in prophylaxis and as therapeutic agents in early reversible stages of cirrhosis. The use of methionine or cystine with casein may be of value.

DR. FRANCIS E. SENEAR: I might take issue with Dr. Michelson that this disease is well known. It is recognized by those who are familiar with the picture; though this patient was admitted because of cirrhosis, two internists failed to recognize any association between the cirrhosis and the lesions of the face. We were able to predict the presence of the hepatitis because of the facial lesions. There is a good deal in the literature about these pulsating angiomas, but it is my feeling that many physicians are not aware of their significance.

Acrodermatitis Atrophicans Chronica. Presented by DR. S. ROTHMAN and (by invitation) DR. Z. FELSHER.

P. O., a white man aged 74, stated that about ten years ago he began to notice some reddening of the feet when bathing. Slowly the redness became permanent, and similar areas appeared on the knees, elbows and dorsa of the hands. He has never had previous cutaneous trouble except calluses, and there is no familial history of cutaneous disease.

Since 1934 he has been treated for tuberculous pleuritis of the right pleural cavity. There is a history of hypertension of about ten years' duration.

The examination reveals diffuse purplish-bluish areas with atrophy of the skin on the dorsa of the feet and hands, knees, elbows and legs. Larger cutaneous and subcutaneous veins shine through the skin. There is a fibrotic cutaneous mass along the ulnar side of the forearms.

The histologic examination of the section removed showed parakeratosis in spots, thinning of the epidermis with partial smoothing out of the rete pegs, thinning

of the corium and dense lymphocytic infiltrate of the corium. The blood vessels were dilated and the vessel walls thickened with swollen endothelial cells. The subcutaneous fat was close to the surface and contained patchy perivascular lymphocytic infiltrates.

The urine showed a slight trace of albumin, with many white blood cells. The blood cell count was normal, and the Kahn reaction of the blood was negative.

Several roentgenograms of the chest in 1934 and 1936 and fluoroscopic examination on Nov. 2, 1945 revealed left-sided pleural effusion.

Livedo Reticularis and Acrodermatitis Atrophicans Chronica. Presented by DR. THEODORE CORNBLEET and (by invitation) DR. H. SCHORR and DR. N. L. BAKER.

M. L., a 54 year old Hungarian born woman, has had prominent veins and redness of the legs for a long time. She said that her mother had the same changes of the skin. Her health has been good. There is atrophy of the skin of the legs, thighs and elbows. Small veins on the thighs and legs are dilated, and there is a bluish red mottling on the buttocks, thighs, legs and feet. The dorsalis pedis and posterior tibial artery pulsations are normal. A roentgenogram revealed the chest to be normal, and the reaction in the Mantoux test was normal.

DISCUSSION ON CASES OF ACRODERMATITIS ATROPHICANS

DR. MAURICE OPPENHEIM (by invitation): The first case shows one of the typical final stages of acrodermatitis atrophicans chronica. Examination revealed a thickening of the skin over the ankles and fixation of the joints of the toes. This stage I called pseudosclerodermatic end stage.

Of more interest in the second case is the livedo reticularis. The majority of dermatologists express the belief that this is connected with syphilis. The presented patient had syphilis. It is my opinion that livedo racemosa need not be a consequence of syphilis. I believe that this is a nevoid disease. One may see it in young and in old persons without any infectious disease and without syphilis. The diagnosis in this second case was also acrodermatitis atrophicans chronica. I have always fought for the fact that acrodermatitis atrophicans chronica is caused by a congenital weakness of the elastic fibers and is a congenital disease which appears later in life, like other nevoid diseases. This combination of livedo racemosa and acrodermatitis atrophicans chronica proves that both diseases are congenital, of nevoid character and genodermatoses.

DR. STEPHEN ROTHMAN: With regard to the second case, I doubt that livedo racemosa is present in addition to dermatitis atrophicans. This woman has a bluish streak at the site of the acrodermatitis, but in acrodermatitis there is a venous stasis. There is no characteristic network of dilated veins.

DR. THEODORE CORNBLEET: We felt justified in making two diagnoses, because portions of the livedo pattern are entirely outside of and distinct from sites of atrophy, the latter being those of acrodermatitis atrophicans. Dr. Rothman's patient is the first I have seen that did not come from Central Europe, that is, if Sweden is not considered part of it.

A Case for Diagnosis (Erythrodermie Pityriasique en Plaques [Brocq]? Dermatitis Atrophicans?). Presented (by invitation) by DR. MAURICE OPPENHEIM.

B.A.W., a salesman aged 43, stated that three years ago he noticed an eruption on the inside of the left thigh, near the inguinal region. The area became scaly, but there was no itching, and later patches on the body appeared.

On the mons veneris, on the epigastrium, two fingers below the umbilicus, and in the left inguinal area, up to the left ischial aspect of the spine, the skin is brownish red in various tinges and the borders are sharp. The surface is covered by branlike scales without infiltration. Diascopy shows almost no change in color. On the left side of the penis there is a red-stained area covered by flakelike scales. On the buttocks and less on the inner surface of the arms there are sharply limited, mostly oval-contoured yellowish red areas, from dime size to palm size. They are covered by flakelike scales, which are adherent. Some of these lesions have no scales, are bluish red and present a sort of translucency of the subcutaneous veins. The skin has fine wrinkles. The face, hands, feet, forearms and legs are free. There are no palpable lymph nodes, and the mucous membranes are free of lesions.

The urine showed 96 mg. of sugar per hundred cubic centimeters. The blood cell count was normal. The nonprotein nitrogen was 40 mg. and the calcium in the serum 8.9 mg. per hundred cubic centimeters.

A biopsy of the right inguinal area showed parakeratosis of the epidermis. The stratum granulosum was partially absent. There was acanthosis. The border between the stratum papillare and the epidermis was sharp; no vacuolization and no spongiosis were present. The papillae were edematous, enlarged and infiltrated with lymphatic elements and many plasma cells. There was an intense infiltration, mostly of round cells, in the cutis which was sharply marginated from the stratum reticulare. In the deeper layer of the cutis round cell infiltration was present around the blood vessels, nerves and glands. The connective tissue in the upper layers was homogeneous, and only little acidophil was present. A few eosinophils were present in the infiltrates.

DISCUSSION

DR. MICHAEL H. EBERT: I thought that this might be a forerunner of some type of lymphoblastoma. The disease is permanent; there is a dull redness, with some evidence of telangiectasia, and there is no sensation present. I do not believe that it is just ordinary seborrheic dermatitis or an irritation dermatitis. I did not see the biopsy specimen.

DR. FRANCIS E. SENEAR: I had the same reaction as Dr. Ebert. On the left side, just above the pubic region, the patient had a definite infiltration. When one examined that closely one saw, in addition to the raised plaque and infiltrate, four nodules that were arranged in a rather arciform fashion, suggesting the type of infiltration that is seen in beginning mycosis fungoides. It could be one of the other lymphoblastomas. The patient gave a history of severe itching, and it is known that patients with the picture of disseminated erythrodermie pityriasique en plaques, which may end as mycosis fungoides, have itching. It is difficult for me to reconcile the presence of these infiltrated plaques with the diagnosis of parapsoriasis.

DR. STEPHEN ROTHMAN: The lesion on the lower part of the chest on the left side is clinically classic parapsoriasis en plaques with the characteristic "pseudoatrophy." I would like to ask whether it has been confirmed that lymphoblastomas later develop in these patients.

DR. SENEAR: Considering the rarity of each of the two diseases under consideration, the en plaque type of parapsoriasis and mycosis fungoides, the fact that there are a number of cases in the literafure reported by competent men as parapsoriasis which have been found later to be mycosis fungoides would mean that this sequence is not uncommon.

DR. HERBERT RATTNER: I think that it was Keil who some time ago observed that the disease in an unusual number of cases of the en plaque type of parapsoriasis eventually became mycosis fungoides. I have forgotten the actual incidence, but it was high.

DR. CARL V. LAYMON, Minneapolis: A few years ago Montgomery and Burkhart of the Mayo Clinic studied a group of these cases and decided that parapsoriasis did not change to mycosis fungoides and that the disease was either one or the other from the beginning and could be recognized as one or the other histologically even in the early lesions. All observers, however, do not agree with this view.

DR. OLIVER S. ORMSBY: I have had experience with 1 patient that illustrates the fact that it takes some time to be sure about the diagnosis. Many years ago I saw a patient with parapsoriasis en plaques. He was wealthy enough to go to Europe and consult Dr. Brocq, who confirmed the diagnosis. There was no doubt that it was his type of the disease. Several years later, however, typical mycosis fungoides developed.

DR. MAURICE OPPENHEIM (by invitation): The clinical picture in this case has puzzled me. The eruption on the body and extremities is the typical picture of parapsoriasis en plaques of Brocq, with circumscribed macular atrophy, but not that in the inguinal and hypogastric area. The skin on the plaques of the trunk and extremities is wrinkled, translucent and yellowish red, with flakelike scales. In the inguinal and hypogastric area there is a bluish red discoloration and infiltration, which Dr. Senear pointed out. There are also small papules which are not sharply outlined. The surface on these areas is smooth, not wrinkled. With the diagnosis of parapsoriasis of Brocq, I had in mind a prestage of lymphoblastoma, as Keil in New York and others have pointed out. It is known that lymphoblastoma cutis can at the beginning simulate psoriasis, eczema, parapsoriasis, lichen planus and the like. There are many polymorphous clinical pictures with which lymphoblastoma can start and only the course of the disease and the histologic observations can prove the diagnosis. I am sorry that not all the discussers saw the histologic picture. There is dense infiltration of the papillary layer and subpapillary layer and a much deeper infiltration following the blood vessels and glands of the cutis and the subcutis. This picture speaks against the diagnosis of parapsoriasis en plaques, and it could be the initial stage of some lymphoblastoma. But I could not see mycosis fungoides cells and no Sternberg Reed cells. Many plasma cells, a few eosinophilic cells and lymphatic elements were present. I am of the opinion that this is a case in which a certain diagnosis cannot be made for the time being.

A Case for Diagnosis (Carcinoma en Cuirasse?). Presented by DR. CLEVELAND J. WHITE.

P.B., a woman aged 50, had had an eruption on the forehead for two months when first observed several weeks ago. She also had an eruption on the left side of the chest, which she stated had been present for two years.

Examination at the present time reveals a thickened indurated area, involving the whole left breast, about 10 inches (about 25.7 cm.) in width. Further examination reveals numerous deep-seated rather yellowish nodules on the right side of the trunk and on the right side of the forehead, with some on the back.

The urine and blood were normal. The blood sugar was 80 mg. per hundred cubic centimeters; the cholesterol was 190 mg., and the Wassermann reaction of the blood was negative.

A biopsy was made, and although the sections were too thick, histologic examination showed the epidermis to be thin and atrophic. There were a large number of nerve bundles in the connective tissue, and the sebaceous glands were absent.

DISCUSSION

DR. HARRY R. FOERSTER, Milwaukee: I was unable to make a confirmatory diagnosis of carcinoma on study of the slide, but I believe that this is a fairly typical clinical example of carcinoma en cuirasse, with metastatic nodules on the forehead and elsewhere. I cannot account for the firm induration and the hard nodules except on that diagnosis. In these cases there is always considerable scar tissue with the carcinomatous infiltration, and it is possible that malignant cells were missed. Another biopsy would probably show carcinoma.

DR. ROBERT C. RANQUIST (by invitation): I would like to suggest as the diagnosis inflammatory nonsuppurative Weber-Christian disease, in which multiple hard nodules are often seen.

DR. EDWARD A. OLIVER: I agree with the diagnosis of carcinoma en cuirasse with metastases. Last week I saw a woman with metastases in the scalp from a recurrent carcinoma of the breast. The picture presented in the scalp was suggestive of lupus erythematosus, with areas of telangiectasia and atrophy, except that there were many indurated nodules scattered through the occipital region.

DR. MARCUS R. CARO: It has been shown that the scalp is a rather common site for metastases from carcinoma of the breast. There have been several biopsies of the scalp in patients at the University of Illinois that demonstrated metastatic carcinomas of the breast.

DR. STEPHEN ROTHMAN: There are a few sites of carcinomas that regularly cause cutaneous metastases, such as the thyroid and prostate glands. The skin of the scalp is practically always involved in generalized cutaneous metastases.

NOTE (March 20, 1946).—Another nodule was removed for study. The report by Dr. J. W. Henry, the pathologist, was as follows: The section of the skin revealed in the corium and subcutaneous tissues extensive tumor deposits of undifferentiated metastatic carcinomatous origin. The observations were consistent with origin in the breast.

Lichen Sclerosus et Atrophicus. Presented by DR. FRANCIS E. SENEAR and DR. MARCUS R. CARO and (by invitation) DR. A. M. BUCHHOLZ.

The patient, a 52 year old Negro woman, was seen in the Department of Dermatology, University of Illinois, on Dec. 28, 1945, with the complaint of an eruption on the skin of the left shoulder and the right breast, of many years' duration.

In the left deltoid region, there was a hard slightly elevated irregularly outlined plaque, the upper half of which consisted of closely set whitish papules. There was central delling of the papules, and the depressions were filled with dark horny plugs. The lower portion of the lesion was apparently keloidal in nature. Nut-sized keloids were present in the presternal region, and there was a bandlike keloid on the right breast, showing central involution.

There was, in addition, a tumor mass within the substance of the right breast, for the treatment of which radical mastectomy was performed on Jan. 3, 1946. Microscopic examination of sections of the tumor showed it to be duct carcinoma.

Histologic examination of a specimen taken from the left shoulder showed a hyperkeratotic scale, with plugging of the follicles. The epidermis was atrophic and flattened. There was intense edema in the upper part of the corium. In the

middle part of the corium and about the follicles lay a dense round cell infiltrate that extended more deeply as a narrow mantle about the blood vessels. The elastic fibers were absent from the edematous upper part of the corium and were fragmented in the deeper parts.

DISCUSSION

DR. CARL W. LAYMON, Minneapolis: This is an unusual case for several reasons, but especially because of its occurrence in a Negro person, which must be rare. Histologically lichen sclerosus has some inflammatory features, and it is conceivable that this inflammation may lead to keloid formation in susceptible persons such as is seen in this patient. I favor the views of Dr. Montgomery and Dr. Nomland that lichen sclerosus is a distinct entity and differs from guttate morphea and atrophic lichen planus. Most patients with lichen sclerosus do not report to a physician until the disease has been present for a long time, so that one sees plaques rather than the early lesions. In this case there was an early lesion on the left wrist in the form of a flat-topped achromatic papule with central plugging.

DR. RUBEN NOMLAND, Iowa City: I think that too much attention has been paid to the plugging in lichen sclerosus et atrophicus. I think that there can be plugging in other diseases, particularly in superficial types of morphea. I thought that this might be superficial morphea with plugging. One could not tell from the section which of the two diseases it was.

DR. OLIVER S. ORMSBY: Originally there was much confusion about this group of diseases. In 1912 I reported the first group of lichen sclerosus in this country (6 patients). This had previously been called white spot disease, which took in scleroderma guttatum, lichen sclerosus and two or three other diseases. I went over all the literature and analyzed the cases and was able to demonstrate to my satisfaction that lichen sclerosus was a clearcut entity, and it was brought out at that time that the term white spot disease would have to be eliminated from the literature.

It is interesting to know that practically all of the work that has been done since confirmed the observations made at that time.

DR. MARCUS R. CARO: There were two points brought up on which I should like to comment. The biopsy was performed in an area that was keloidal in appearance. It showed the histologic characteristics, however, of lichen sclerosus. Dr. Nomland said that it was difficult to differentiate this disease histologically from morphea. I thought, in examining the section in this case, that the wide zone of edema just below the atrophic epidermis was diagnostic of lichen sclerosus et atrophicus. This subepidermal zone of edema is not seen in morphea.

Syringocystoma. Presented by DR. LOUISE E. TAVS (by invitation).

C.B., a white woman aged 20, presents an eruption which appeared seven years ago as small nodules on the neck. The lesions have gradually increased in number and size, involving the anterior portion of the neck, the axillas, the anterior aspect of the chest and the pubic and crural regions. They are asymptomatic.

On examination there are skin-colored and yellowish oval nodules of fleshy consistency, which vary from 3 to 7 mm. in diameter.

The histologic examination of a section taken from a nodule in the pubic area showed syringocystoma.

DISCUSSION

DR. M. J. REUTER, Milwaukee: One cannot make a definite diagnosis in this case except by microscopic examination. I accept, however, the diagnosis of

syringocystoma. I think that the location is unusual. The lesions are situated commonly over the anterior part of the trunk, and the patients are for the most part young women.

DR. RUBEN NOMLAND, Iowa City: I think that there are two types of syringocystoma. The first, which this patient presents, is a widespread nevoid type, occurring early in life. The second type occurs in women in the forties and is usually limited to the lower eyelids. Both are typical enough clinically so that they can be recognized, and both show a typical histologic picture.

DR. OLIVER S. ORMSBY: In the histologic section it was described as syringocystadenoma, but clinically it was called syringocystoma, which is an entirely different disease. It is characterized by pearly nodules and occurs on the face and on the eyelids and other areas. The areas are often extensive. I have seen it on the abdomen and trunk. I have seen the sweat glands so involved that the patient did not perspire and the perspiration could not be collected for examination. Our patient was treated with roentgen rays; the skin became normal, and perspiration was restored.

Syringocystadenoma is located on the sides of the neck and on the chest. It has been mistaken for multiple benign cystic epithelioma when it has occurred on the face. This case is clinically and histologically an example of syringocystadenoma.

Melanoderma. Presented by DR. L. F. WEBER and DR. IRENE NEUHAUSER.

G.R., a quarry worker aged 53, first noticed pigmentation on his forehead about six months ago. For twenty-five years he has removed stone from an open excavation about 100 feet deep. A pneumatic hammer loosens and breaks the stone. The pneumatic hammer is not oiled by the patient, but is oiled by another person.

He has many follicular plugs on the extensor surfaces of the fingers, back of the hands and wrists. The forearms and arms show a bluish pigmentation which is follicular and diffuse. The forehead shows diffuse pigmentation which varies from bluish to blackish. The cheeks and nose show a brownish pigmentation with follicular localization.

It is interesting to examine the pigmented areas with Wood's filter.

DISCUSSION

DR. EDWARD A. OLIVER: This is an exceptional case of melanoderma. I would rather leave the explanation as to what has produced the melanin pigmentation to Dr. Weber.

DR. HARRY R. FOERSTER, Milwaukee: This case is similar to one presented by Dr. Ormsby at the last meeting. Both are cases of occupational melanoderma. In Dr. Ormsby's case there were inflammatory lesions prior to the development of the pigmentation. In that case the patient worked indoors, there was no history of actinic exposure and the pigmentation was probably postinflammatory. In this case the man works outdoors in a quarry, exposed to sunlight and is in contact with grease and oil when using a pneumatic hammer. Some ingredient of the oil has apparently produced photosensitivity.

DR. CLEVELAND J. WHITE: In some cases of melanoderma there is a history of exposure to oil fumes alone.

A Case for Diagnosis (Folliculitis? Dermatitis Herpetiformis?). Presented by DR. FRANCIS E. SENEAR and DR. MARCUS R. CARO and (by invitation) DR. M. J. BRUNNER.

Localized Scleroderma (Saber Blade Type). Presented by DR. DAVID V. OMENS and (by invitation) DR. HAROLD D. OMENS.

Boeck's Sarcoid. Presented by DR. MICHAEL H. EBERT and (by invitation) DR. M. KAGEN.

C. S., a Negro woman aged 31, was well until three months ago, when brownish red papules appeared on the forehead and then on the chin, cheeks and ears. There are flat reddish brown papules on the forehead, nose, cheeks, chin, ears and the posterior aspect of the neck and over the manubrium sterni.

The urine and blood were normal. The Kahn reaction of the blood was negative. The roentgenogram of the chest showed enlargement of the hilar lymph nodes, with accentuation of the bronchial markings extending out from the hili. The roentgenograms revealed the hands and feet to be normal. The reaction to the Mantoux test in dilution of 1 to 10,000 was negative.

DISCUSSION

DR. H. E. MICHELSON, Minneapolis: I have nothing new to add except that to me it was interesting to compare the roentgenogram of the chest with that in the case of blastomycosis. To my untrained eye they seemed to be similar. Roentgenologists are willing to make the diagnosis of sarcoid on observations in roentgenograms of the chest, and some of them are willing to make a diagnosis of blastomycosis. Certainly blastomycosis, sarcoidosis and tuberculosis of the lung give a similar appearance in the roentgenogram of the chest.

DR. FRANCIS E. SENEAR: I was sorry that Dr. Stillians did not discuss this case, because several years ago we went out to the Municipal Tuberculosis Sanitarium and one of his friends and colleagues gave an excellent discussion of sarcoid. Dr. Beilin, the roentgenologist at Augustana Hospital, discussed the roentgenologic aspects. He showed slides of the three diseases which Dr. Michelson mentioned. That was the first time I heard an internist discuss sarcoid from a comprehensive standpoint. The physician who was there that night representing orthopedic surgery had never heard of sarcoid as applied to orthopedic surgery until he started to look it up and found that Singling's disease, osteitis tuberculosa multiplex, which he had known well, was a manifestation of sarcoid.

DR. MICHELSON: I saw a woman recently whose active manifestations of sarcoid were papule-like elevations on the dorsum of the toe. She went to an orthopedist, who advised amputation of the toe. I had seen the woman many years before for a plaque on the face, and we were able to associate the two diseases, a biopsy from each being characteristic of sarcoid.

DR. HERBERT RATTNER: In Mexico cases of leprosy were shown that were clinically indistinguishable from sarcoid.

DR. IRENE NEUHAUSER: I believe that cases of sarcoid have been observed which later developed into the tuberculoid type of leprosy.

A Case for Diagnosis (Chronic Granuloma? Granuloma Inguinale?). Presented by DR. THEODORE CORNBLEET and (by invitation) DR. H. SCHORR and DR. N. L. BAKER.

R. C., a Mexican girl, aged 14, is mentally defective. She fell four months ago and bruised her buttocks. Since then, she has been in bed, but has been unable to say when the present lesions appeared.

On each buttock, there was a large sharply outlined flat raised granular plaque. The right one measures 10 by 15 cm., the left 20 by 10 cm. Near the natal cleft, there is a similar smaller lesion.

The examination of the blood showed 2,650,000 erythrocytes and 4,350 leukocytes. The Kahn reaction of the blood was negative. The urine showed albumin (2 plus). The Wright stain preparations of tissue juice pressed from the lesions showed short bacillary bodies in large mononuclear cells, somewhat resembling Donovan bodies.

DISCUSSION

DR. HARRY R. FOERSTER, Milwaukee: Certain features of the disease in this case suggest artefacts. The lesions are sharply marginated, as though a line had been drawn along the edge of each. The corners were angular instead of rounded as in most inflammatory granulomas, and both lesions were about identical. I wonder whether this child actually had an injury, and, if so, whether the injury might not have been repeatedly mutilated to prevent healing and to provoke sympathy, since she is mentally defective. The observation of Donovan bodies may be incidental.

DR. MARCUS R. CARO: I had occasion to see the sections, and I agree with Dr. Foerster that anything even resembling Donovan bodies had no connection with the disease. The histologic changes were those of a chronic granuloma, but there was nothing to suggest granuloma inguinale.

DR. THEODORE CORNBLEET: Organisms resembling Donovan bodies were seen in the lesions by laboratory personnel. (They did not say actual Donovan bodies.) The possibility of artefacts was thought of, but fixed dressings did not result in improvement of the lesions. They were given careful attention by the surgeons, without showing the slightest change. They are bizarre and unlike anything I ever saw.

Hemorrhagic Telangiectasia. Presented by DR. MICHAEL H. EBERT and (by invitation) DR. N. L. BAKER.

Systemic Blastomycosis. Presented by DR. THEODORE CORNBLEET and (by invitation) DR. D. COHEN and DR. N. L. BAKER.

L. H., a 44 year old Negro woman, first noticed pain in the right knee a month ago. Three days later a nodule appeared over the right supraorbital ridge, which later broke down and discharged thick yellow pus. Several more furuncle-like lesions appeared on the face, trunk and extremities in rapid succession. Some of the lesions did not break down, but took on a verrucous appearance. There are multiple lesions now on the face, trunk and extremities. Double refractile budding spheres are observed in direct examination of the pus.

A roentgenogram of the knees showed no abnormality, but one of the chest showed miliary infiltration in both pulmonary fields. There is an occasional nonproductive cough, and she complains of poor appetite and weakness. Her temperature ranges between 99 and 102.5 F.

DISCUSSION

DR. ARTHUR W. STILLIANS: I was interested in this patient because I have a patient with similar disease under treatment. My patient came to the Municipal Tuberculosis Sanitarium presenting only a few lesions on the forehead. The organism was observed in the cutaneous lesions, and the pulmonary observations were positive. Other results were negative. He was given large doses of

potassium iodide for many months. The lesions disappeared, and he was apparently in normal condition. Then iodide acne developed, and soon afterward bilateral orchitis with hydrocele. No blastomycetes were seen in the seminal or hydrocele fluid. Sulfapyridine was given for two weeks, then an attempt was made to resume treatment with the iodide. This had to be abandoned, because of sensitization. A course of oxophenarsine hydrochloride with roentgen ray therapy given locally was followed by subsidence of the orchitis. Since then he has taken copper sulfate by mouth in dilute citric acid sweetened with saccharin and is apparently normal.

I shall be glad to hear what treatment does for the patient presented today.

DR. THEODORE CORNBLEET: We thought immediately of an eruption from bromides and blastomycosis. On simple direct examination the blastomycetes were seen in profusion, so that the diagnosis was easily made. This patient also has a carcinoma of the stomach.

Some of the cutaneous blastomycoses are utterly resistant to iodides, in common with the systemic variety. Dr. Martin of Duke University expressed the belief that his vaccine is useful for this group, that by its administration the patient is, as he says, desensitized and then becomes susceptible to the favorable action of iodides.

Congenital Defects Following Maternal Rubella During the Early Months of Pregnancy. Presented by DR. DAVID V. OMENS and (by invitation) DR. HAROLD OMENS and DR. M. S. KAGEN.

L. R., a 14 month old girl, was born with bilateral cataracts, cardiac disease and mental retardation. Rubella had developed in the mother of the infant during the first two months of pregnancy.

In a recent article by Albaugh of California (*J. A. M. A.* **129**:719 [Nov. 10] 1945), who cited Gregg and Swan of Australia, 134 cases of congenital defects are reported, showing that rubella occurring during the first two months of pregnancy will cause pathologic changes in 100 per cent of the offspring. Fifty per cent of the infants are affected if the mother has rubella during the third month of pregnancy. The pathologic changes caused by maternal rubella are bilateral cataracts, cardiac disease and cerebral agenesis.

The blood was normal. Studies of the chemical content of the blood showed calcium 9.5 mg. and phosphorus 4.3 mg. per hundred cubic centimeters.

DISCUSSION

DR. CARL W. LAYMON, Minneapolis: As Dr. Omens mentioned in the history, congenital defects following maternal rubella have been reported in the literature. Most dermatologists, however, have had little experience with such cases. Recently I asked an obstetrician and a pediatrician concerning termination of pregnancy in the event that rubella occurs in the early months of pregnancy, and it was their opinion that the pregnancy should be terminated if rubella occurs in the first trimester.

DR. HERBERT RATTNER: This was a timely presentation, for the subject, to judge from its growing literature, is an important one. Reports indicate that if a woman has rubella in the first three months of pregnancy, her infant is likely to be born with a serious congenital defect, such as bilateral glaucoma with resultant blindness, cataracts, cardiac lesions and mental defects. The exact number of such accidents is not known, but the incidence is high enough so that the occurrence of rubella in the first three months of pregnancy should constitute an indication for therapeutic abortion.

The whole subject is relatively new. All the facts are not yet analyzed; even obstetricians and pediatricians have not yet crystallized their opinions. However, a dermatologist may be the one to observe the rubella in early pregnancy and may have to share in the decision as to whether pregnancy should be terminated.

Malignant Melanoma. Presented by DR. EDWARD A. OLIVER and (by invitation) DR. SAMUEL M. BLUEFARB.

M. J., a large woman aged 58, had a pigmented mole on the right cheek. Following a sunburn last summer and within a short time a number of granulating excrescences developed on the mole. It looked like granuloma pyogenicum, but she stated that it bled little. Examination of a histologic section showed it to be a highly malignant melanoma.

While melanomas are being discussed, I would like to call attention to a recent article by Pack in *Surgery*, June 1945, on the surgical treatment of melanomas. Dr. Pack not only removes the melanoma with a wide and deep surgical excision, but he dissects out the lymphatic vessels, running from that area to the glands, and the lymph nodes as well. He expressed the belief that in that way many persons who would otherwise die from metastases can be saved.

My ideas as to what advice to give a person with a blue mole or a deeply pigmented lesion have changed considerably since I saw a girl of 17 several weeks ago with a deep blue melanotic mole on the back of her hand. This mole had been present all her life, but just a week before I saw her it had begun to bleed and ulcerate. It had not been irritated. It was immediately excised rather widely, and the pathologist reported it to be a malignant lesion that had already begun to metastasize. Following Dr. Pack's suggestions, the surgeon excised the axillary nodes, which, fortunately, showed no metastases.

In the future I intend to advise my patients to have any suspicious blue or deeply pigmented lesion excised with a rather wide and deep excision.

DISCUSSION

DR. STEPHEN ROTHMAN: Like Dr. Becker I differentiate lentigo maligna or intraepidermal melanoma from the invasive malignant melanoma. In the first case broad surgical excision effects complete cure. In patients with malignant melanoma the surgeons at Albert Merritt Billings Hospital excise the lesion broadly and extirpate the lymph nodes of the whole region. Not a single patient has yet been saved in this way. I do not believe that biopsy has any ill effect.

DR. MAURICE OPPENHEIM (by invitation): In considering biopsies in melanomas and melanotic wart, it is known that biopsy sometimes stimulates the growing of melanoma. Therefore, one should be a little careful and make a total excision, particularly in cases of blue nevi.

METROPOLITAN DERMATOLOGICAL SOCIETY

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Feb. 18, 1946

Erythema Nodosum, Probably Produced by Drugs. Presented by DR. LESLIE P. BARKER.

Persistent Papule of Scabies. Presented by DR. MAURICE J. COSTELLO.

DISCUSSION

DR. LESLIE P. BARKER: The location of the eruption, the intense itching and the residual pigmentation would suggest a case of dermatitis herpetiformis, but there were no active lesions and no scarring. There were several papules on the dorsa of the hands that were angular, flat topped and violaceous, suggesting lichen planus. I think that a biopsy should be made of one of those lesions.

DR. F. G. TICE (by invitation): Altogether, the facts fit best with the diagnosis of dermatitis herpetiformis. He has had injections at the Postgraduate Hospital, the nature of which I am not sure, but they may have been for lichen planus.

DR. MAURICE J. COSTELLO: I think that this patient has the papular type of dermatitis herpetiformis. The localization of the grouped papules and the changes in pigmentation speak for it. The response to sulfapyridine is a strong point in favor of that diagnosis. I think that the papular type of dermatitis herpetiformis is usually not easily diagnosed. Patients who present dermatitis such as this patient has should have a therapeutic test with sulfapyridine. A tablet or two a day may keep the eruption under control.

SAN FRANCISCO DERMATOLOGICAL SOCIETY

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March 1, 1946

A Case for Diagnosis (Bowen's Disease of the Eyelid? Lupus Erythematosus?). Presented by DR. CHARLES W. MCNITT, Reno, Nev.

A Case for Diagnosis (Tinea Versicolor? Parapsoriasis?). Presented by DR. FRANCES M. KEDDIE.

A Case for Diagnosis (Tertiary Syphilis of the Thigh?). Presented by DR. GRANT MORROW (by invitation).

A Case for Diagnosis (Histoplasmosis?). Presented by LIEUTENANT EDWARD J. RINGROSE (by invitation).

B. H., a 24 year old naval officer, was admitted to the United States Naval Hospital, Oakland, Calif., on Jan. 2, 1946, complaining of a swollen area beneath her left eye. She first noticed a 1.5 cm. bluish spot under the left eye in May 1945, while on duty at Charleston, S. C. Roentgenologic studies showed no change in the bones in this region at that time. The bluish spot, at first flat, was followed by gradually increasing swelling, but was not accompanied with pain. There was moderate tenderness to firm pressure. A basal metabolic rate in November was —17 per cent, and she took 2 grains (0.13 Gm.) of thyroid from that time until the second week in January 1946. About this time she noticed firm tender areas over the posterior aspects of both arms, just proximal to the elbows. These were similar to the lesion beneath the left eye. During her present hospitalization lesions have developed on the posterior and anterior aspects of both thighs, the anterolateral aspect of the left arm and in the gluteal region. There

has been no loss of weight, and her general health has been good except for occasional headache and a slight vaginal discharge of six months' duration. Her highest temperature (oral) during hospitalization was 99.2 F.

Results of the physical examination were within normal limits except for the cutaneous lesions, which were described as follows: Beneath the left eye was an area of edema about 5 cm. in diameter. The central portion of this was firm and tender, and the overlying skin showed a smoky violaceous discoloration.

In the posterior aspect of each arm, just above the elbow, was a similar edematous plaque, which was somewhat more indurated and slightly larger than the facial lesion, and the overlying skin here was somewhat mottled pink, white and violaceous.

There were smaller similar lesions on the anterior aspect of the left arm, the left forearm, the anterior and posterior aspects of both thighs and the inferior aspects of both gluteal regions.

Striking characteristics of all lesions were moderate firmness and tenderness.

She has received only the thyroid given elsewhere and three treatments with roentgen rays, 140 r each, to the lesion beneath the left eye, from Dec. 20, 1945 to Jan. 9, 1946, a total of 420 r to this area. No regression has been noted. The lesion has gradually increased in size.

Repeated blood cell counts gave normal results. The serum proteins, bleeding time and coagulation time were normal. Reactions to "brucellergen" (a suspensoid of nucleoprotein from Brucella cells), tuberculin, histoplasmin and coccidioidin intradermal tests were negative. Cultures from aspirations of lesions showed no growth. The agglutination reactions for Proteus OXK and X19 were negative. Roentgenograms of the chest, sinuses, spine, elbows, hands, wrists and feet showed no deviation from the normal. The basal metabolic rate was —17 per cent on January 8 and —8 per cent on January 17.

A guinea pig was inoculated intraperitoneally with juice from a lesion. After two weeks the animal was killed. Results of the histologic examination were essentially negative except for occasional reticuloendothelial cells of the liver, which contained multiple small oval cytoplasmic bodies which were basophilic and averaged 1 to 2 microns in size. In the spleen occasional bodies of a similar nature were present in the reticuloendothelial cells of the pulp.

A section from the infiltrated area of the left elbow was reported as follows: Present in the subcutaneous tissue about occasional sebaceous glands and small nerve bundles, as well as being most numerous about small arterioles, were collections of round cells. In several small arterioles there was proliferation of lining endothelial cells with obliteration of the lumen. Contained within a few of the endothelial cells, as well as in some of the mononuclear phagocytes, were small oval to coccoid bodies. Most of these stained with hematoxylin, although a few stained poorly and were slightly refractile. Some had a resemblance to Toxoplasma organisms, and others resembled granules of extruded chromatin material. Some of the isolated tiny blue bodies were surrounded by a small amount of homogenous pink-staining material. A few resembled somewhat Leishmania forms. Further studies are necessary for final diagnosis.

DISCUSSION

DR. FREDERICK G. NOVY JR.: I saw this patient in Oak Knoll Hospital one month ago. The clinical appearance is about the same now. I thought that at that time she had a deep type of sarcoid (Darier-Roussy). The fact that the reaction to the tuberculin test was negative tends to confirm that diagnosis. The roentgenologic observations did not help. Roentgenograms were made of the long

bones and chest. I feel that she probably has sarcoid, regardless of the report of biopsy.

DR. REES B. REES: I also considered the diagnosis of Darier-Roussy sarcoid, but rejected it. The lesion on the left arm, particularly, was intradermal, and the skin had a pigskin-like appearance, which indicated intradermal edema. The lesion below the eye is rather diffuse, and there is little body to it.

DR. HIRAM E. MILLER: I would like Dr. Ringrose to tell us about the protozoan-like organisms which were seen.

LIEUT. EDWARD J. RINGROSE (by invitation): Dr. D. A. Wood, the pathologist, spent about a hundred hours looking at sections. One piece of tissue was macerated for N. N. N. culture (protozoa). In the biopsy specimens from the patient and in the animal tissues studied spheroid bodies with a central basic staining body and a peripheral clear capsule-like zone were seen. Protozoan-like organisms with motile forms were present in the N.N.N. mediums, along with some peculiar encapsulated forms and spheroid bodies, looking something like Histoplasma capsulatum. Different stains showed similar organisms. Clinically it may be a sarcoid. Sections, however, rule that out. She was seen several months ago before a tumor board. At that time it was concluded that the lesion beneath her left eye might be a hemangioma. On the basis of this, she was given three treatments with roentgen rays, a total of 420 r, to the lesion below the left eye. No change in the lesion was obtained.

DR. HIRAM E. MILLER: I was particularly interested in this case, especially when protozoan-like organisms were mentioned. Purpuric and hemorrhagic lesions are described in histoplasmosis. The reaction to the histoplasmin test was negative, but this is not unusual for histoplasmosis. Further attempts should be made to rule out this diagnosis.

Atypical Acne Vulgaris, Confined to the Ears. Presented by DR. OTTO E. L. SCHMIDT.

W. L. D., a white schoolboy aged 16, was seen in the Dermatology Clinic of the Stanford University Hospital, complaining of an eruption of both ears of six months' duration. No symptoms were noted. Prior treatment was with the "electric needle," one roentgen radiation, ointment and attempted extraction with a comedo extractor. The past history was not contributory except for excessive ingestion of milk, eggs and fried foods.

The skin of the face is somewhat seborrheic and a few tiny comedos are present. On the helix of both ears are numerous large comedos and white milia. The affected tissue is slightly hypertrophied and slightly tender on manipulation.

Treatment with sulfur and resorcinol paste and 30 per cent sulfur ointment has had no appreciable effect.

DISCUSSION

DR. CHARLES W. MCNITT: When the lesions were opened, did the contents shell out as milia do?

DR. NORMAN EPSTEIN: I believe that these lesions are those of milia in an unusual location. Acute actinic dermatitis may have preceded the development of these lesions.

DR. OTTO E. L. SCHMIDT: The boy has not been sunburned, and there is not anything that he can think of which could have predisposed him to development of these lesions.

DR. FREDERICK G. NOVY JR.: In following out Dr. Alderson's thought of cleanliness, as far as these lesions are concerned, Dr. Miller has suggested that the boy may have acne from the use of oil on his hair. He may have had a latent nevus, which has become more prominent with adolescence. However, the presence of nevi on both ears would be unusual.

Scleroderma en Bande, Improved with Treatment with Pancreatic Extract. Presented by DR. ARNE E. INGELS.

A Case for Diagnosis (Granuloma Annulare? Sarcoid?). Presented by DR. ERVIN EPSTEIN.

A Case for Diagnosis (Hereditary Hemorrhagic Telangiectasia?). Presented by DR. ARNE E. INGELS.

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

LEWIS B. ROBINSON, M.D., *Chairman*

SAMUEL M. PECK, M.D., *Secretary*

March 5, 1946

Folliculitis Abscedens et Suffodiens (Folliculitis Decalvans?). Presented by DR. OSCAR L. LEVIN.

H. P., a white man aged 25, first noticed a "cyst" in his scalp in November 1943, while in the Army. This lesion was removed surgically in February 1944. In April 1945 a new "cyst" appeared and was followed by other similar lesions, many of which drained pus. Local applications of penicillin and other drugs were ineffectual. The eruption was diagnosed as folliculitis abscedens et suffodiens, and he was hospitalized. For five months he received various forms of treatment, including treatment with penicillin solutions, roentgen rays (1160 r to the scalp) and an autogenous vaccine (streptococci and staphylococci). The scalp showed progressive improvement, and the patient was discharged in January 1946. He was first seen at the Beth Israel Hospital on January 14.

At the time of examination there were numerous depressed atrophic areas throughout the scalp, varying from 0.5 to 2.5 cm. in diameter. Subsequent examinations showed numerous reddish pinhead-sized inflammatory pustules located at the follicular orifices. These had not been present at the time of first observation. These apparently primary lesions, together with the general appearance of the scalp, were more suggestive of the diagnosis of folliculitis decalvans than of folliculitis capitis abscedens et suffodiens.

DISCUSSION

DR. ISADORE ROSEN: If this is a case of perifolliculitis abscedens et suffodiens, there are certainly no manifestations at this time. The history of sebaceous cysts of the scalp rather than that of communicating abscesses also speaks against the diagnosis.

DR. LOUIS TULIPAN: With the history of infection and the type of scar this man presents, I believe that the picture is more that of folliculitis decalvans than of perifolliculitis abscedens et suffodiens.

DR. OSCAR L. LEVIN: While the patient was in the Army, a diagnosis of folliculitis abscedens et suffodiens was made. My diagnosis was folliculitis decalvans. The first diagnosis was not accepted by me, because of the absence of evidence indicating the presence of abscesses, sinuses and irregular disfiguring scars. The scalp presented small spots of alopecia with superficial smooth scars.

Hereditary Edema of the Legs. Presented by DR. OSCAR L. LEVIN.

W. B., a man aged 65, was first seen at the Dermatologic Clinic of Beth Israel Hospital in January 1946. For the past forty-one years the patient has had chronic lymphedema of both legs. For the past thirty years he has also had more than twenty attacks of erysipelas, necessitating frequent hospitalization. The patient stated that his father had unilateral edema of the leg, which developed suddenly, and that his mother always had "swollen legs."

Examination shows exteme swelling from the toes to the knees of both legs. Pitting edema can be demonstrated with ease. The skin around the ankles is erythematous and slightly scaly. Scars from old operative procedures may be seen near the right patella. The inguinal glands are slightly enlarged.

The specific gravity of the urine ranged from 1.018 to 1.025, with a trace of albumin. The blood cell count showed 6,510,000 red cells, with 112 per cent hemoglobin. The white cell count was 10,000, with 64 polymorphonuclear leukocytes, 30 lymphocytes, 2 staff cells, 3 monocytes and 1 eosinophil. The erythrocyte sedimentation rate was 12 mm. in one hour. The blood culture was sterile. The total protein was 5.42 Gm., albumin 3.48 Gm. and globulin 1.94 Gm. (ratio 1.79). The blood glucose was 115 mg. and the nonprotein nitrogen 33 mg. per hundred cubic centimeters. The Wassermann reaction of the blood was negative. Roentgenograms of the legs showed no pathologic changes in the bones and no signs of osteomyelitis. Cultures and smears from the edema fluid of the legs failed to reveal organisms.

DISCUSSION

DR. LOUIS CHARGIN: First glance at this case would suggest Milroy's disease, inasmuch as the swelling is bilateral, but closer observation would, I think, rule out this disease altogether. The patient is 65; he said that the trouble appeared thirty years ago, first on one leg and then on the other; he gave a history of syphilis and of infections due to operation on the leg. It seems to me that lymph stasis following infection is the underlying factor and that it is not Milroy's disease.

DR. DAVID BLOOM: Hereditary lymphedema of the lower extremities may be congenital, or it may appear in the second decade. A number of cases are reported which started later in life. I believe that the patient has hereditary lymphedema, although it developed in the third decade. Many patients with this disease give a history of frequent attacks of erysipelas-like inflammation of the legs. This can be explained by the fact that the accumulated lymph fluid furnishes a good medium for the growth of streptococci. The origin of infection is the toes, which are close together because of the edema, giving rise to injury of the skin between the toes and dermatophytosis.

DR. E. W. ABRAMOWITZ: In my experience most cases of symmetric elephantiasis are due to Milroy's disease. The patients with this disease are subject to recurrent attacks of lymphangitis, which causes further enlargement of the affected parts. I have found penicillin ointment the most satisfactory remedy for the control of these recurrent attacks of lymphangitis in Milroy's edema and also elephantiasis nostras.

DR. OSCAR L. LEVIN: I do not agree with Dr. Chargin that the lymphedema resulted from attacks of erysipelas. The history indicates that the patient previously had repeated attacks of infection of the left leg, which showed scars from incisions. He had suffered from erysipelas, but the right leg was also swollen and enlarged, and the lymphedema of this leg could not have resulted from infection in the other leg. The history also indicated that his father had had enlarged legs. Milroy's disease may not be evident at birth, but may appear later in life, even in the third decade. Benzyl penicillin will be used in the treatment of the disease in an attempt to combat infection, if present.

Pityriasis Rubra Pilaris. Presented by DR. JESSE A. TOLMACH.

Sarcoid of Boeck. Presented by DR. OSCAR L. LEVIN.

Lupus Erythematosus. Presented by DR. JESSE A. TOLMACH.

Larva Migrans. Presented by DR. BEATRICE M. KESTEN.

D. R. H., a boy aged 2½, is presented from Vanderbilt Clinic, with an eruption on the right thigh of six weeks' duration. The patient returned from Florida eight weeks ago; two weeks later an eruption on the right leg was noted, which has cleared up in one area only to reappear in another.

There is a fine erythematous line on the anterior aspect of the right thigh which describes a complete loop and then wriggles down the thigh about 3 cm. The end of the erythematous line contains a few vesicles.

DISCUSSION

DR. ISADORE ROSEN: This is a typical example of larva migrans, but there are instances in which generalized eruptions develop clinically, simulating scabies or papulovesicular urticaria associated with larva migrans. Such cases are recognized in the South but, as a rule, not in the North.

DR. LOUIS TULIPAN: I also saw a case of that kind, but the patient originally presented the typical picture of larva migrans. The eruption started on the back and covered it entirely from the neck to the popliteal space. He had been treated while in the Army. He also showed the type of eruption mentioned by Dr. Rosen, but he had a typical linear arrangement here and there. It is possible that he also had a secondary infection from the terrific itching and consequent scratching.

BRONX DERMATOLOGICAL SOCIETY

Wilbert Sachs, M.D., *President*

Henry Silver, M.D., *Secretary*

Oct. 17, 1946

Rat Mite Dermatitis Due to Liponyssus Bacoti (Hirst) (Kodachrome Slide Presentation). Presented by DR. MARION B. SULZBERGER and (by invitation) DR. A. A. FISHER.

M. J., a Negro woman aged 40, came to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital in December 1944. She gave a history of having had an eruption for two years and of having been treated for

urticaria at another hospital. She had received various diets and injections of calcium, without any effect.

When first seen, the patient presented an eruption which was fairly generalized and consisted of urticarial lesions and some lichenified papules in the cubital area. Treatment with injections of "hapamine" (a chemical combination of histamine and despeciated horse serum globulin) was of little benefit.

In June 1945 the patient stated that she had seen some minute crawling "insects" on her body and that her mother was suffering from a similar eruption. The patient then brought in a mite. This mite and others which were collected in the patient's home were identified as Liponyssus bacoti (Hirst).

Rickettsialpox Due to Allodermanyssus Sanguineus (Kodachrome Slide Presentation). Presented by DR. MARION B. SULZBERGER and (by invitation) DR. A. A. FISHER.

J. S., a man aged 35, first noticed an "insect" bite on the left great toe on Oct. 1, 1946. The lesion had a central vesicle and a surrounding red border. The vesicle soon became pustular and then necrotic. Chills then developed, and the temperature rose to 104 F. Four days later a generalized papular eruption appeared. The initial lesion healed, and a chickenpox-like scar was left. There were no sequelae from the generalized eruption.

Many of the papular lesions were capped by a tiny vesicle. There were also present a few bright red erosions on the tongue.

Mice mites belonging to the Allodermanyssus sanguineus group were discovered in the building in which the patient resides. An unidentified rickettsial organism was obtained from the mites. Serum from the patient's blood yielded the same organism.

At the height of the fever the patient's white blood cell count was 4,500, with 40 per cent lymphocytes and 60 per cent polymorphonuclear leukocytes.

The patient had an uneventful recovery.

DISCUSSION OF FOREGOING TWO CASES

MR. CHARLES POMERANTZ, entomologist (by invitation): Mites belong to the class Arachnida and are of the order Acarina. The larger members of this order are known as ticks, and the smaller ones are referred to as mites. My interest in ticks and mites is mainly in their great propensities for bearing disease to human beings and animals.

Dr. Fisher observed a case in which he suspected the disease of being due to insect bites and suggested that I make a survey of the home of the patient to determine what that insect might be. After the examination I discovered a mite, later identified as Liponyssus bacoti (Hirst). This mite has been implicated and experimentally proved as the vector of endemic typhus in this country.

On July 19 and 20, 1946, the daily papers carried the news of a strange outbreak of fever in Kew Gardens, Long Island, N. Y. Ticks were suspected. A survey proved that ticks could be ruled out as the cause of this illness. The dispersion of this illness throughout the sixty-nine buildings comprising the development and the ecologic factors necessary for the development of disease-bearing ticks, together with other pertinent factors conspicuous by their absence, suggested an entirely different disease-bearing arthropod. It was deduced that it must be a mite, one that can travel from apartment to apartment and be carried by a host,

such as mice or rats, through the hollow structure of walls and floors and be deposited adjacent to apartment walls. Subsequently, mites were discovered on the walls of apartments and incinerators and in other nooks and corners. Mice leavings, both old and fresh, and live mice were seen on the top and bottom parts of the incinerators.

In cooperation with the Division of Insect Identification of the United States Department of Agriculture, my specimens were identified as Allodermanyssus sanguineus (Hirst). I was informed that this mite is capable of attacking man and causing dermatitis similar in nature to that caused by its relative Liponyssus bacoti (Hirst).

Comparing the clinical symptoms of the disease in persons in the Regency Park development with the symptoms occasioned by the bite of other mites in this and other countries, Dr. Huebner and Dr. William L. Jellison, parasitologists of the United States Public Health Service, came to the conclusion that in this mite lies the vector of a new and hitherto undescribed disease, later named rickettsialpox.

It is important, in the eradication of the disease, to stress that measures must be taken to rid the home or apartment house of mice and rats. General cleanliness and adequate rat proofing and mouse proofing are suggested.

Dr. Harry Keil (by invitation): The eruption in the Negro woman was originally diagnosed as eczematosus dermatitis. It resembled lichenified eczema, and she was treated for this disease for many months, without benefit. About two years ago, while the patient was in my care, I learned that her mother and a cousin, who was living with her temporarily, had also become affected with a similar eruption. The patient stated that her apartment was heavily infested with rats and complained of "little things" that were biting her. She brought in several specimens, and on microscopic examination I thought that one was a mite. On another occasion I saw a mite on the patient's body, and at the point where it was engorged I could see a wheal arise, which was transient. Treatment with "hapamine" (a chemical combination of histamine and despeciated horse serum globulin) was unsuccessful. Subsequently, the case was turned over to Dr. Fisher for further study.

Dr. Theodore Rosenthal: During the height of the outbreak in Queens, N. Y., I had the opportunity of seeing a number of patients. All presented disseminated papular lesions which did not resemble any dermatosis with which I am familiar. It seemed to me, also, that the disseminated lesions resembled the initial lesion, although they were somewhat smaller. Each lesion seemed to have a central punctum, while some had tiny vesicles. My impression was that it was a cutaneous response to an insect or mite bite. I did not then know the causative agent.

Dr. Nathan Sobel: Dr. Rosenthal invited me to see a few of the patients. From a distance the disseminated lesions strongly resembled chickenpox, but closer examination revealed that there were no "dew drop" vesicles of chickenpox. The lesions were the size of a pinhead and mostly papular, and each was surrounded by a red areola. The general eruption appeared ten days later than the initial lesion, which resembled an insect bite. The patients were sick and had chills and high temperatures for from seven to ten days. I understand that there were no sequelae and no complications and that all recovered. Liponyssus bacoti was named as a vector of typhus in 1931 by Shelmire and Dove (*J. A. M. A.* **96**:579 [Feb. 21] 1931) and was described as a mite that bit the infected rat and then transmitted the rickettsia to human beings.

DR. WILBERT SACHS: Some time ago I observed a series of such cases in New Jersey. The causative agent was recognized and confirmed at Washington, D. C., and the cases were reported on by Lowell (Rat Mite Dermatitis: Acariasis Caused by the Tropical Rat Mite, Liponyssus Bacoti Hirst, ARCH. DERMAT. & SYPH. **54**:278 [Sept.] 1946). The disease was observed in women who were working in a factory. They complained of an itching eruption limited to the abdomen, and some had a slight rise in temperature. The eruption was traced to rats, and after extermination no new cases appeared and the disease in the old ones cleared entirely. Lowell reported that these were the first cases observed in the eastern part of the United States.

DR. A. A. FISHER (by invitation): The eruption due to rat mites consists of punctate hemorrhagic lesions, which on healing leave chickenpox-like scars. About 150 patients have been seen with this type of eruption. Each initial lesion has a satellite lesion. The inguinal as well as the cervical glands are enlarged. In addition, a generalized eruption appears, which is ushered in by profuse sweating and leukopenia. This eruption is either papular or varicelliform. The initial lesion leaves a scar, and the ensuing ones do not. This serves to differentiate this eruption from chickenpox. A few patients presented mucomembranous lesions, and occasional eroded areas were noted on the tongue.

The eruption in the Negro woman is apparently the first case of rat mite dermatitis observed in the eastern part of this country.

A Case for Diagnosis (Sarcoidosis?). Presented by DR. CHARLES WOLF.

H. W., a woman aged 65, born in the United States and married, stated that her father died of pneumonia at the age of 59, her mother died at the age of 92, two sisters died of cancer, one brother died of a disease of the spleen and the other brother died of a cardiac ailment.

The patient was well nourished and presented discrete pale pink to chamois-colored nodular lesions, varying in size from that of a split pea to that of a hazelnut. The first lesion appeared about six months ago on the right lower eyelid. The lesions on the body appeared shortly thereafter.

The Wassermann and Mazzini reactions of the blood were negative. Examination of the stool revealed no parasites or ova. Examination of the chemical content of the blood revealed 22 mg. of urea nitrogen and 90 mg. of sugar per hundred cubic centimeters of blood. Examination of the blood revealed 4,300,000 red blood cells and 8,900 white cells with 68 per cent polymorphonuclear leukocytes, 30 per cent lymphocytes and 2 per cent eosinophils.

Roentgenograms of the gastrointestinal tract revealed no abnormalities. Roentgenograms of the chest showed a pleural effusion of the base of the left lung. Thoracentesis of the left side of the chest was performed on Sept. 12, 1946, and 50 cc. of a straw-colored fluid was obtained. The fluid was cultured and was observed to be sterile. The cell count revealed 1 lymphocyte.

Histologic examination (Dr. W. Sachs) showed throughout the cutis an epithelial mass arranged in individual cells and clumps of cells. In the deep layer of the cutis a large part of this mass was around the sweat apparatus. In many places these cells appeared to be arranged in linear fashion, simulating sweat ducts. In one or two areas there were similar strands of these cells emanating from the lower border of the epidermis. The cells were somewhat cuboid in shape, with

round deeply stained nuclei. There was no inflammatory reaction. The observations suggested a nevus of the sweat apparatus.

DISCUSSION

DR. DAVID BLOOM: The disease in this case resembles erythema elevatum diutinum more closely than any other dermatosis. Some time ago I presented a case at the Manhattan Dermatologic Society, which was reported on by Combes and Bluefarb (ARCH. DERMAT. & SYPH. **42**:441 [Sept.] 1940), in which there were also lesions on the ear and the back closely resembling lesions of xanthoma.

DR. HERMAN SHARLIT: The observations in this case suggest granuloma annulare. What does the microscopic examination disclose?

DR. LOUIS CHARGIN: The following possibilities must be considered: (1) granuloma annulare, (2) erythema elevatum, (3) sarcoid and (4) metastatic carcinoma. In granuloma annulare the lesions are not so solid. The lesion of erythema elevatum has a solider border, but I doubt whether the infiltration or mass in that disease is as great as it is in this patient. Against sarcoid, of course, is the color and whiteness of the lesion; however, I would not be willing to rule it out purely on clinical grounds. One may observe such solid lesions in metastatic carcinoma. I cannot, however, reconcile the pathologic changes. I would suggest that further study be made of the histologic features in this case.

DR. WILBERT SACHS: I was aware of all the possibilities presented in this case. Dr. Wolf discussed the case with me, and I looked into each possibility but could find no evidence to substantiate any. I thought of granuloma annulare or sarcoid as a clinical diagnosis, but there was nothing in the slide to corroborate either diagnosis. There was a neoplasm throughout the skin, and in the deep part of the cutis sweat glands were seen with epithelial cells, suggesting a nevus or neoplasm of the sweat gland apparatus.

DR. CHARLES LERNER: Several lesions impressed me as being of localized scleroderma, especially because of the color and consistency. It is conceivable that this is a neoplasm, and, as Dr. Sachs intimated, it may be a sweat gland tumor.

DR. WILBERT SACHS: The observations as revealed in the slide are unquestionable, but there may be questions about my interpretation. I am sure that many of the diagnoses that were suggested on clinical grounds are not substantiated by the histologic changes. This patient does not have sarcoid, sarcoma or granuloma annulare. She has an epithelial neoplasm, and I think that further studies should be made by other pathologists. They might interpret the observations differently.

DR. HENRY SILVER: In a difficult case of this type one would look for and expect to obtain aid from the histologic examination. The histologic observations, however, are at variance with the clinical impression. The disease is extremely difficult to interpret, yet one should, at least tentatively, attempt a diagnosis. Dr. Chargin covered the differential diagnosis thoroughly. The reason that he objected to the diagnosis of granuloma annulare was that the lesions of granuloma annulare are not so solid. However, in the best article on the subject, Arndt (*Arch. f. Dermat. u. Syph.* **108**:229, 1911) differentiated several types of granuloma annulare. He described one of the varieties in which the lesions are extremely hard and of ivory color and ivory consistency. Some of the lesions in the case presented are annular, with hard scleroderma-like borders. Erythema elevatum diutinum and

sarcoid can be ruled out on clinical grounds. Further histologic studies should be made of the smaller and younger lesions.

DR. ARTHUR SAYER: This is an unusual case and presents many difficulties in diagnosis, as was brought out in the discussion. The age of the patient favors the diagnosis of a malignant disease rather than granuloma annulare or erythema elevatum diutinum; the latter two are most frequently encountered in younger persons.

DR. MARION B. SULZBERGER: I would suggest to Dr. Wolf that he obtain more tissue, have several histologists examine the sections and then report on this case.

DR. CHARLES WOLF: I would like to stress the highlights in this case. The patient had none of these lesions six months ago. The multiple lesions occurred on the entire body simultaneously. The striking feature is the profound infiltration that exists; the lesions might perhaps be compared with epitheliomas, which may be as hard. I recall that several years ago Dr. Spiegel presented a patient with a nasal lesion which was unusually hard and which was later diagnosed as epithelioma. There are no signs of epithelioma except for loss of weight. True, the lesions are only of six months' duration, but if the patient had a visceral carcinoma there would have been some definite evidence of it by this time. I agree with Dr. Sachs's suggestion that further studies should be made by other pathologists.

A Case for Diagnosis (Scleroderma-Like Process of the Back?). Presented by DR. LOUIS CHARGIN.

M. K. aged 62, married and a salesman, has mild diabetes (under control), coronary insufficiency and early cerebral arteriosclerosis.

Recently, without any assignable reason, there appeared a hardening of the skin of the back covering the region from the base of the hair line on the neck to the belt line on the back. The area of hardness is deep and does not pit, and the skin cannot be raised into folds. The entire skin of the back is reddish, especially at the borders of the affected skin. There are no subjective symptoms.

The Wassermann reaction of the blood was negative. The blood cell count showed no abnormalities. The cholesterol content was 240 mg. per hundred cubic centimeters of blood.

Histologic examination showed no significant changes except for slight edema of the upper part of the corium.

DISCUSSION

DR. DAVID BLOOM: The almost boardlike hardness of the involved area makes me favor the diagnosis of dermatomyositis, in contrast to Buschke's disease.

DR. CHARLES LERNER: The lesion is too hard for Buschke's disease and not hard enough for scleroderma. I think that there is a metabolic disturbance.

DR. LEO SPIEGEL: My father had a similar condition many years ago. It disappeared after many months. He was diabetic, and in diabetic persons infiltrations of this sort occur. This lesion is of a chronic nature, involves the deeper portions of the skin and usually follows trauma. It is a low grade infection and may well be scleredema of Buschke.

DR. ADOLPH ROSTENBERG: I think that the consistency and clinical features of the lesion are in favor of Buschke's disease.

DR. WILBERT SACHS: I would suggest that if another biopsy is done, the specimen be taken from the deep tissues. The present histologic observations rule out scleroderma. It is difficult to diagnose scleredema microscopically. The slide shows only edema in the upper portion of the cutis.

DR. ARTHUR SAYER: I agree with Dr. Bloom's suggestion of dermatomyositis as a probable diagnosis. However, I feel that a biopsy down to underlying muscle is essential for making a definite diagnosis.

DR. HENRY SILVER: The process strongly suggests scleredema of Buschke. There is a history of a mild infection of the throat preceding the appearance of the hardness. In favor of the diagnosis is also the beginning of the edema on the neck, spreading down to the back.

DR. HARRY KEIL (by invitation): I think that this is a typical case of scleredema of Buschke. Often pathologists cannot diagnose this disease. There is nothing really too definite about the pathologic observations.

DR. LOUIS CHARGIN: Evidently one first thinks of the possibility of Buschke's disease in this case. It is certainly not dermatomyositis. Buschke's disease begins with an episode of fever, continues for a few months and then disappears. This process has already existed about six months and is gradually progressing. Except for diabetes, the patient is well. I do not feel that the condition under discussion has any relation to the diabetes in this patient.

Parapsoriasis en Plaques. Presented by DR. MARION B. SULZBERGER and (by invitation) DR. JOHN GARB.

M. B., a man aged 30, registered at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Sept. 16, 1946, presenting lesions of one year's duration. He had measles, mumps and rubella during childhood, Vincent's infection of the mouth at the age of 14 and bursitis of the shoulder joints at the age of 27. The patient stated that the eruption fades partially at times, but does not entirely disappear. His general health has been good. He is obese, measuring 5 feet 6¾ inches (166.8 cm.) in height and weighs 223 pounds (101.4 Kg.).

The eruption is symmetric, is located on the trunk and extremities and is most pronounced on the abdomen, flanks and the lower part of the back, while the legs are almost entirely devoid of lesions. The lesions are superficial, ill defined and not infiltrated. The areas of the lesions vary from the size of a small pea or a bean to large and diffuse. The skin is dry and covered with fine scaling, and in some areas, especially on the sides of the chest and the flanks, it is wrinkled and atrophic, giving the impression of a faint network. The lesions on the abdomen are yellowish red, while those on the flanks are slightly purplish red. Diascopic pressure does not produce any change in color. The inguinal and axillary lymph nodes are not enlarged.

The Wassermann reaction of the blood was negative. The urine had a specific gravity of 1.035, and there were calcium oxalate crystals. The hemogram revealed 5,900,000 erythrocytes and 15.8 Gm. of hemoglobin per hundred cubic centimeters of blood (95 per cent). The differential count was normal except for 10 per cent eosinophils.

The histologic section was examined by Dr. Charles F. Sims, and the diagnosis was parapsoriasis. The epidermis was somewhat irregular, with scattered areas of parakeratosis. Basal cell liquefaction was observed at many points. Exocytosis

was visible, and there was a diffuse perivascular cellular reaction, composed for the most part of small round cells. There was moderate interstitial edema in the collagen and in the upper part of the corium.

DISCUSSION

DR. JOHN GARB (by invitation): The patient is presented for the purpose of discussing possible treatment, because the disease is known to be resistant to all forms of treatment. Dr. Wise and I have treated a number of patients with parapsoriasis en plaques with the fluid diphtheria toxoid and with diphtheria toxoid, alum precipitated. All patients responded favorably except 1 patient who presented lesions clinically typical of parapsoriasis en plaques, but a histologic section revealed the structure of lymphoblastoma.

DR. ADOLPH ROSTENBERG: It seemed to me that the lesions were too small to warrant a diagnosis of parapsoriasis en plaques. In my experience no form of treatment has been of benefit in this disease.

DR. DAVID BALLIN: The remarks of Dr. Rostenberg, with which I am in accord, respecting the smallness of the lesions would rule out parapsoriasis en plaques.

DR. HARRY KEIL (by invitation): I am inclined to accept the diagnosis. A patient under my observation had parapsoriasis en plaques for five years and is now presenting the pathologic changes of mycosis fungoides.

DR. HENRY SILVER: The diagnosis of parapsoriasis en plaques can be accepted in this case because of the characteristic areas on the thighs and the trunk. The lesions of the guttate or Jadassohn type are usually smaller, involve chiefly the upper extremities and the trunk, show fine scaling and resemble maculopapular syphilitic lesions.

DR. ARTHUR SAYER: I believe parapsoriasis en plaques to be the correct diagnosis. One of the important points to be considered is the absence of itching, which is a significant point in differentiation from mycosis fungoides.

DR. WILBERT SACHS: I agree with the clinical and microscopic diagnosis of parapsoriasis en plaques. There were no large cells and no other features of mycosis fungoides revealed in this slide.

DR. MARION B. SULZBERGER: This patient is presented in the hope that the therapeutic effect of diphtheria toxoid will be demonstrated. Will Dr. Garb present the patient again after a course of this treatment?

DR. FRANK E. CROSS: Is diphtheria toxoid in the nature of a nonspecific remedy?

DR. JOHN GARB: One can see typical large patches of parapsoriasis en plaques on the dorsal surfaces of the feet and large diffuse areas on the flanks.

I cannot answer with certainty the question raised by Dr. Cross as to the action of diphtheria toxoid. It may stimulate the adrenal glands, an opinion advanced by Dr. Collier and Dr. Oberdoerffer in the treatment for leprosy with diphtheria toxoid (Milestones in Leprosy, *J. Thailand Research Soc.* **12**:177 [Feb.] 1940). Dr. Wise and I have used it in patients with chronic eczema, pemphigus, mycosis fungoides and in a patient with mycosis fungoides with bullous lesions (Wise, F.: Experimental Therapy with Diphtheria Toxoid in Four Cases, ARCH.

DERMAT. & SYPH. **45**:784 [April] 1942). I used it experimentally later in patients with sarcoid, exudative discoid and lichenoid chronic dermatosis, mycosis fungoides and many other dermatoses. Good results were obtained in some cases.

Before the toxoid is used, the patient is tested for hypersensitivity with the Moloney technic. If there is no reaction, 0.5 cc. of diphtheria toxoid is injected subcutaneously every ten to fourteen days, depending on the response. Improvement may be noted after the first, second or third injection. Localized painful swelling and fever develop in some patients.

Dermatitis Herpetiformis Benefited by Suramin Sodium. Presented by DR. DAVID BLOOM.

S. M., a man aged 30, registered at the Skin and Cancer Unit of the New York Post-Graduate Medical School on April 1, 1946, presenting an eruption of four and a half years' duration. The eruption was generalized, vesicular and crusted. The lesions were discrete or appeared as rings or serpiginous figures. The eruption was associated with severe pruritus.

For the past four and a half years the patient has received many kinds of treatment and responded well to arsenic and sulfapyridine. He received sulfapyridine for about three years, 2 tablets a day (1 Gm.), which kept him almost free of the eruption for about one year. At the Skin and Cancer Unit he received acetarsone, extract of liver, calcium and autohemotherapy, without any benefit. Fever therapy cleared the eruption, which recurred within a few days after the patient left the hospital.

After treatment with intramuscular injections of suramin sodium was started, 0.25 Gm. once a week, the patient began to notice relief from itching. After seven injections of suramin sodium were given, the eruption began to clear except for a few lesions on the back, legs and scalp. The patient has received to date eleven injections, and thus far the eruption has not recurred.

Laboratory examinations, which included a blood cell count, a differential count, an examination of the urine and Wassermann and Kahn tests revealed no abnormalities.

DISCUSSION

DR. RUDOLF L. BAER: An interesting feature in this case, besides the result achieved with suramin sodium is that considerable benefit was observed at first with the use of sulfapyridine, but later the drug had no effect.

I have recently observed a woman with severe dermatitis herpetiformis, whose disease also appeared to be controlled with sulfapyridine for about eight weeks, but then the drug was no longer effective.

DR. ADOLPH ROSTENBERG: I have used sulfadiazine with good results in patients with this disease. In 1 patient under my care, whose disease could not be differentiated from pemphigus, treatment with sulfadiazine cleared the lesions completely, and the patient remained well for a long period. I regard the effect of the drug almost as a differential diagnostic point between pemphigus and dermatitis herpetiformis.

DR. CHARLES REIN: Although patients with dermatitis herpetiformis may be helped considerably with suramin sodium, it would be wiser to employ milder and safer medicaments, such as sulfadiazine and solution of potassium arsenite, until more is learned about the untoward reactions following the use of suramin sodium.

The indiscriminate and routine use of this drug may cause serious reactions, especially when it is administered for a chronic recurrent disease.

DR. CHARLES A. GREENHOUSE: In my recent experience, treatment of 6 patients with suramin sodium has given uniformly poor results. In most of these patients there developed early albuminuria accompanied with other toxic symptoms.

In the case presented I regard the present condition as a remission. Thyroid, which has also been advocated as of benefit in this disease, has proved useless in my hands. It must be remembered that this disease is characterized by remissions and that some of the benefits ascribed to the use of certain drugs represent such remissions.

DR. DAVID BLOOM: The favorable result thus far obtained in this case is not decisive as to the value of suramin sodium in the treatment for dermatitis herpetiformis. I prefer the intramuscular to the intravenous route, because with the latter toxic by-effects are more likely to be produced. The dosage I employ is 0.16 Gm. as the first dose and then 0.25 Gm. at weekly intervals. The blood and the urine are examined frequently for indications of nephritis or granulocytopenia.

Lichen Nitidus. Presented by DR. DAVID BALLIN.

PHILADELPHIA DERMATOLOGICAL SOCIETY

J. M. Schildkraut, M.D., *Chairman*

Douglass A. Decker, M.D., *Secretary*

Oct. 18, 1946

Lichen Ruber Planus; Lichen Planus Hypertrophicus of the Leg. Presented by DR. DONALD M. PILLSBURY and (by invitation) DR. IRA L. SCHAMBERG.

Atopic Dermatitis? Presented by DR. W. N. NEW, United States Naval Hospital (by invitation).

Exfoliative Dermatitis of Leiner. Presented by DR. FRED D. WEIDMAN and DR. LOUIS GOLDSTEIN.

R. I., a white boy aged 1 year and of good general appearance, presents a seborrheic disease of the scalp. Elsewhere there are expansive bilateral and symmetric plaques of scaly erythroderma. The margins are sharp. There is no evidence of exudation. The scales exfoliate in sheets in some places, as on the soles. At birth the patient was apparently normal. At the age of 3 weeks a papulopustular eruption began on the abdomen, coalesced and spread. There was a purulent discharge from the conjunctivas and nares. In a few weeks the child became emaciated and there were only a few islands of normal skin. There were dry seborrheic crusts on the scalp, vegetations in the intertriginous regions, bullae on the palms and soles and erythroderma elsewhere. The child is well nourished now; he has been given a special nutritional regimen.

Seven serologic tests for syphilis were made; all results were negative except the Kolmer reaction, which was 4 plus on Nov. 30, 1945, and the Kahn reaction,

which was positive on December 4. Four tests subsequent to December 14 elicited negative reactions. The albumin-globulin ratio was normal. Examinations of the blood revealed mild anemia and slight leukocytosis. There was no evidence of syphilis in roentgenograms of the long bones. Fungi could not be demonstrated in scales from the skin. In the feces, there were bacteriologic flora which are normally observed.

The histologic picture was not distinctive, but suggested parapsoriasis.

Improvement resulted from applications of methylrosaniline chloride, solution of aluminum acetate and solution of potassium permanganate. In December, 280,000 units of penicillin were administered. The dermatitis was moderately improved.

Primary Exfoliative Dermatitis; Leiner's Disease; Congenital Ichthyosiform Erythroderma. Presented by DR. M. H. SAMITZ.

W. H., a white boy aged ten weeks, ill nourished and looking sick, presents a universal eruption, characterized by scaling and exfoliation which are most prominent on the palms and soles. No pustular element is present. There is faint diffuse erythema. The patient, who was born with a completely cleft palate, is said by the family physician to have had a generalized pustular process on the skin five days after birth, which began on the face. This did not improve with treatment, but the pustular element disappeared and generalized exfoliation occurred. A corneal ulcer developed in the right eye on Sept. 27, 1946, and one developed subsequently in the left eye. Since his admission to the hospital there has been no significant change. The family history is irrelevant. The mother's Wassermann reaction of the blood was negative.

The urine was normal. The Wassermann reaction of the blood for syphilis was negative. A blood cell count revealed 57 per cent of hemoglobin, 3,410,000 erythrocytes and 8,700 leukocytes. Roentgenograms of the bones revealed no indication of syphilis. On October 14, the calcium content of the blood was 5.1 mg. and the phosphorus was 1.2 mg. per hundred cubic centimeters; on October 15, the amounts were 10.3 and 1.1 mg., respectively.

Before admission to the hospital the patient received penicillin "local ointment" and ultraviolet rays; after admission penicillin was applied to the eye and given parenterally (discontinued October 8), with colloidal baths, olive oil and two whole blood and two plasma transfusions, with no noticeable improvement in the skin.

DISCUSSION

DR. FRED D. WEIDMAN: In criticism of the diagnosis for our patient, this youngster is in a good state of nutrition, whereas a large percentage of children with exfoliative dermatitis of Leiner are emaciated and die before they reach this stage. The disease did not begin in the usual place, and nothing is mentioned in texts, in so far as I was able to learn, about the symmetric and bilateral distribution. I doubt that many instances of more exquisite symmetric distribution have been seen. Every little jagged edge of a plaque on one side of the body seemed to have its counterpart on the other side. The condition is certainly not Ritter's disease. There is not the infiltration in Ritter's disease that there is in the eruption in this child; there is only extremely superficial exfoliation. Dr. Goldstein said that the normal ratio of the albumin and globulin was a point against a diagnosis of Leiner's disease. I doubt that one can count so much on such a variable factor as the protein content of the blood in children of this age. I do not believe that the

protein content of the blood ought to be given so much weight. At first I thought that the disease in this patient was ichthyosis, but the more I studied it, the more I realized that the symmetry and the seborrheic type of lesion on the scalp were not consistent with ichthyosis. I agree with the diagnosis for the second patient presented. I think that his disease is classic in all respects.

DR. EDWARD F. CORSON: If one studies the disease in the 2 patients who were given the same diagnosis, I think that differences can be seen. W. H. definitely has exfoliative dermatitis, whereas I doubt that R. I. has that disease. R. I. has symmetric and sharply marginated patches, on the surface of which there is no exfoliation, but there is a seborrheic crust. The eruption looks more like psoriasis, with a seborrheic distribution and covering instead of the typical scale.

DR. H. H. PERLMAN: Was generalized moniliasis eliminated as a possibility in R. I.?

DR. FRED D. WEIDMAN: Moniliasis was excluded by laboratory methods.

DR. LOUIS GOLDSTEIN: I saw R. I. a few months after he was treated by the pediatrician, and at that time his disease was much worse than it is now. When I saw him first he had generalized dermatitis. There were but a few islands of normal skin. On the palms and soles there was a nonpurulent discharge, and there were suppurating fissures at the angles of the mouth. The reaction of the blood to a serologic test for syphilis was positive, but later checking of the serologic results revealed them to be irregularly positive. Observations for syphilis were negative in both the mother and the father. However, syphilis could be ruled out in the baby because the reaction of the blood to the serologic test was negative before treatment with penicillin was instituted, there was no enlargement of the spleen and the long bones did not show syphilitic involvement. I thought of the possibility of Leiner's disease, but this child was not breast fed. There was an article in *The Journal of Pediatrics* (**26**:367 [April] 1945) in which there was reported a reversal in the albumin-lobulin ratio in a series of cases. In this case the ratio was normal.

DR. H. H. PERLMAN: In Leiner's original paper all the babies—43 in all—were breast fed; but Brenneman showed that Leiner's disease can occur in babies who are not breast fed.

DR. MORRIS MARKOWITZ: The histologic picture of R. I. corroborates Dr. Corson's opinion. The lesion looks like one of psoriasis, and I should like to support Dr. Corson's diagnosis of psoriasis.

DR. BERNARD L. KAHN: R. I. presents neurologic symptoms, such as twitching of the neck and shaking of the head, and I wonder whether there is a neurologic explanation for the lesions.

DR. JOSEPH V. KLAUDER: R. I. impressed me as being a moron, but what has that to do with the dermatologic picture? I cannot associate the dermatologic disease with the possibility of retarded mental development.

DR. FRED D. WEIDMAN: I think that any one with a condition of the skin like this child's would perhaps seem moronic. R. I. does bang his head, as children will do from temper or in resistance to what is being done to them; after all, children do bang their heads. As to the histologic picture, Dr. Markowitz mentioned a pertinent point. The changes are largely those of psoriasis, and the sharp margination of the plaques does not rule out parapsoriasis en plaque. I was amazed when I looked at the section from W. H., the child with the marasmic

condition—again there is a picture of parapsoriasis. In both cases the histologic picture of parapsoriasis is presented. Of course, the histologic picture alone does not constitute an entire clinical entity, but it does make one consider the possibility of parapsoriasis in an infant.

DR. THOMAS BUTTERWORTH (Reading, Pa.): In the case of R. I., the possibility of congenital ichthyosiform erythroderma of the localized type should be considered. The yellowish greasy scale is common in that disease.

Lupus Erythematosus. Presented by DR. I. ZUGERMAN.

Dermatitis Herpetiformis. Presented by DR. PATRICIA DRANT.

Occupational Leukoderma (Pinta?). Presented by DR. JOSEPH V. KLAUDER and DR. MARJORY K. HARDY.

P. S., a Mexican man, has worked for the same manufacturing company for the past twenty-eight years. His work consists of cleaning tanks with a caustic solution. He has always worn rubber gloves or mitts when working. He had no cutaneous disease until the spring of 1945, when "brown and white spots" appeared on his hands and later on his nose and ears. It is alleged that other workers, also Mexicans, experienced a similar condition while wearing gloves.

On the dorsa of both hands, extending to the lower third of the forearms, there are depigmented areas. The palms are unaffected. There are some hyperpigmented areas. There are patches of hyperpigmentation on the tip of the nose and on the ears.

Patch tests were performed on large areas of the upper arms ten days ago, both with rubber mitts worn at the time the condition started and with gloves which have been worn since. The patches were removed tonight.

DISCUSSION

DR. FRED D. WEIDMAN: Pinta should be considered. The patient is a Mexican, from central Mexico. There is slaty discoloration of the ears, in addition to the vitiligo-like lesions on the hands. There have been 3 cases reported in the United States as cases of pinta, but in none of those was the spirochete demonstrated. Dr. Pardo-Castello was shown a patient at the Philadelphia General Hospital, and he stated that the case was a classic illustration, clinically, of pinta, but repeated examinations (dark field, four or five times and with great care) failed to demonstrate the spirochete. I saw demonstrations of the technic used in the examination for spirochetes while I was visiting in Habana, Cuba. The margin of the lesion must be selected and a fold of the skin pinched up with heavy hemostatic forceps until serum exudes. It is a harsh procedure, but it is necessary to demonstrate the organism before one makes a final diagnosis of pinta, especially when the disease occurs in a patient in this country. I should say that the disease in this patient would bear further study.

DR. HERMAN BEERMAN: In support of Dr. Weidman's statement are the triangular areas of depigmentation on the wrists.

DR. H. H. PERLMAN: I saw many cases of pinta in Mexico a year ago. The physician used a razor blade, scarified the surface and demonstrated the spirochete. My first impression was that this was a case of pinta, and when I learned that the patient was Mexican my impression was confirmed. The disease looks like typical pinta.

DR. JOSEPH V. KLAUDER: We have been unable to obtain the type of antioxidant used. If the disease is pinta, it is remarkable that it should appear in the areas confined to contact with his gloves. We were told that several fellow workers have similar changes affecting their hands. In the original contribution of Oliver and Schwartz, the disease occurred in Mexicans and Negroes and lesions appeared on the face and ears. The dermatosis in our patient is improving. The lesions now lack the ivory white appearance at the site of the depigmented areas. I think that the aforementioned circumstances oppose the diagnosis of pinta. Moreover, the patient left Mexico twenty years ago and has not returned.

NOTE.—A later dark field examination of serum obtained by scarification yielded negative results. The Kahn reaction was negative. The Wassermann reaction was weakly positive.

Ulcers of the Legs Associated with Sickle Cell Anemia. Presented by DR. CLARENCE S. LIVINGOOD and (by invitation) DR. MALCOLM SPENCER.

CLEVELAND DERMATOLOGICAL SOCIETY

Harley A. Haynes, M.D., *President*

George W. Binkley, M.D., *Secretary*

Oct. 24, 1946

A Case for Diagnosis (Acanthosis Nigricans? Epidermodysplasia Verruciformis?). Presented by DR. R. C. LIGHT, DR. J. KAM and DR. A. E. WALKER (service of DR. H. N. COLE and DR. J. R. DRIVER).

Generalized Sarcoidosis. Presented by DR. R. C. LIGHT, DR. J. KAM and DR. A. E. WALKER (service of DR. H. N. COLE and DR. J. R. DRIVER).

Aleukemic Lymphocytosis Cutis (Lymphocytoma of the Skin). Presented by DR. E. W. NETHERTON.

Dermatitis Vegetans. Presented by DR. R. C. LIGHT, DR. J. KAM and DR. A. E. WALKER (service of DR. H. N. COLE and DR. J. R. DRIVER).

Occupational Keratoses and Carcinoma of the Face in a Negro Man. Presented by DR. R. C. LIGHT, DR. J. KAM and DR. A. E. WALKER (service of DR. H. N. COLE and DR. J. R. DRIVER).

Pigmented Purpuric Lichenoid Dermatitis (Gougerot's Disease) (Hypostatic Dermatitis?). Presented by DR. R. C. LIGHT, DR. J. KAM and DR. A. E. WALKER (service of DR. H. N. COLE and DR. J. R. DRIVER).

A Case for Diagnosis (Idiopathic Edema?). Presented by DR. E. W. NETHERTON.

J. L., a white man aged 62 and employed as a punch press operator, was seen for the first time on Sept. 12, 1946. He had been married for nineteen years, had one child living and well and had enjoyed good health until about August 1. At

that time a swelling of the dorsal surface of the hands and fingers, face and scalp suddenly developed. This swelling extended down onto the neck. At the onset there was intense pruritus. There were periods of partial remission of the edema, but it had never completely disappeared. Large and small doughlike nodules and ridges appeared on the scalp, particularly in the occipital region. These doughy areas were pruritic, with spontaneous remission, which was followed by the development of other similar lesions. For the past twenty years the patient had had brief attacks of painful swelling of the joints, particularly of the knees and ankles. During the past three weeks the edema of the hands had decidedly decreased. However, nodules of doughy consistency had developed on the dorsal surface of the hands, and firm nodules, with apparent involvement of the bone, had appeared at some of the metacarpal joints. There was a small skin-colored papule on the tragus of the right ear; this has been considered as possibly a tophus of uric acid. There have been no constitutional symptoms and no recent acute infections of the upper part of the respiratory tract. The temperature has remained normal.

The hemogram showed normal red and white blood cell counts, with a normal differential count. The level of uric acid was 3.5 mg. per hundred cubic centimeters, and the cholesterol in the blood was 147 mg. per hundred cubic centimeters four hours after the patient had eaten. The Wassermann and Kahn reactions of the blood were negative. The basal metabolic rate was —2 per cent. Roentgenologic examination of the skull showed no abnormalities. A roentgenogram of the cervical aspect of the spine revealed decided hypertrophic changes of the vertebrae. A roentgenogram of the chest showed no abnormalities.

Tissue was removed from a nodule on the scalp and also from the edematous area of the face, on the left margin of the lower jaw. The histologic changes observed were essentially the same in both specimens and were as follows: The epidermis was normal. Throughout the corium there was loose arrangement and fragmentation of collagen fibers. There were many fibroblasts and small poorly stained collagen fibers throughout the section. Many areas showed myxedematous degeneration. There were a few small foci of perivascular lymphocytic infiltration in the corium.

DISCUSSION

DR. W. R. HUBLER (Youngstown, Ohio): My first thought was that it might be one of the rare parasitic diseases, such as infection with Loa loa or filariasis. However, the patient has never been out of this country and the results of biopsy do not indicate one of these parasitic diseases. In the lower portion of the section there is an area of degeneration, staining of which might be revealing.

DR. H. N. COLE: I did not get a chance to ask him whether he had had recurrent attacks of erysipelas. I agree with the chairman about the cutis on the back of the head, although it was rather more indurated than one would expect. Is his metabolic rate low?

DR. E. W. NETHERTON: It is —3 per cent. I do not know what this man has. He has edema, which came on suddenly, apparently overnight. I am sure that the folds in the scalp are of short duration, because when he came they were about twice as large as they are now. A biopsy was made of one of these folds. He had pitting edema of the dorsal surface of the hands, eyes and forehead. There was no pitting of the face. When I first saw him I thought that he had myxedema. His hair, however, is of fine texture and is oily, his basal metabolic rate is normal, the onset was sudden and the cholesterol in the blood is within normal limits. There are deposits of some sort of salts in the metacarpal bones. He has a slightly elevated level of uric acid in the blood. It must be some sort of unusual edema.

He has had no acute infection of the upper part of the respiratory tract, no recurrent erysipelas and no infections of the nasopharynx. He has had no muscular pains like those seen in myositis. He has taken no drugs. He has lived without any change in his routine, occupation or recreational activities. He has improved about 50 per cent from the time I first saw him. However, the nodules continue to form and disappear, lasting for two or three days to a week.

DR. H. A. HAYNES JR.: Could it be some type of localized myxedema?

DR. E. W. NETHERTON: That is usually associated with hyperthyroidism, usually recurrent hyperthyroidism. This man has never had hyperthyroidism, and therefore he could not have a recurrence. The sections are usually more myxomatous in that disease. I think that some special staining should be done, as Dr. Hubler suggested, and that will be done this next week.

DR. G. A. DEOREO: This certainly does not have the clinical appearance of periarteritis nodosa, in which one of the commonest observations is edema, particularly of the hands. This disease is seldom diagnosed in life. It might be that this patient has this disease.

DR. E. W. NETHERTON: The hemogram revealed no abnormalities. He has had no fever.

DR. H. J. PARKHURST (Toledo, Ohio): I believe that the diagnosis of lymphoblastoma should still be entertained.

A Case for Diagnosis (Lichen Planus? Lymphoblastoma?). Presented by DR. E. W. NETHERTON.

Hodgkin's Disease of the Cervical Lymph Nodes, with Cutaneous Infiltrations. Presented by DR. H. D. POCOCK JR. (by invitation).

Chronic Myeloid Leukemia with Leukemia Cutis. Presented by DR. H. D. POCOCK JR. (by invitation).

Purpura Annularis Telangiectoides. Presented by DR. DON R. PRINTZ (from the office of DR. H. N. COLE and DR. J. R. DRIVER).

Mrs. C. A., a white woman aged 38, is presented complaining of an eruption on the extremities that is now pruritic. The patient has been working strenuously since the spring of this year, converting an old farm house into a modern home. She gave no history of taking medicine and stated that she feels well.

Physical examination reveals an eruption confined almost exclusively to the extremities, although there are a few lesions on the buttocks. The eruption is made up of sharply defined purpuric spots, varying in size from 3 mm. to 12 mm. in diameter. They have no particular shape; some of them are irregular, and occasional ones are circinate. Many form circles, being about 1 cm. in diameter and clearing in the center. Some of the lesions are telangiectatic, and a fine adherent whitish scale covers them. The older lesions are brownish red. There are lesions also on the dorsum of the feet and around the ankles, and there is one lesion on the hand. There is no evidence of atrophy and no evidence of scratching.

The hemogram disclosed no abnormalities, and the urinalysis revealed no albumin or sugar.

Histologic examination of a specimen from a lesion on the inner aspect of the right thigh showed a slight increase of keratin, with atrophic epidermis. The

papillary layer was flattened in places. There was a slight increase of fibrous tissue. There was a slight perivascular increase of histiocytes and an infiltration of lymphocytes. The corium was thin. In the superficial part of the corium there were small foci of free red blood cells, which were mixed with connective tissue fibers. There was no proliferation of the capillary walls, and no hemosiderosis was present.

DISCUSSION

DR. H. G. MISKJIAN: I should like to call attention to the fact that the essential histologic changes in purpura annularis are in the capillaries. Under the name of capillaritis the French School has grouped together a number of diseases and syndromes, known by various names, whose characteristic lesions are seen in the capillaries of the skin. There are different anatomic types of capillaritis. Pigmented purpuric lichenoid dermatitis (Gougerot's disease) represents the proliferating type, with proliferation of the endothelial cells and consequent thickening of the capillary walls. Purpura annularis is an example of the telangiectatic type of capillaritis and belongs in the same group as angioma serpiginosum.

DR. H. N. COLE: At the meeting of the Los Angeles Society a year ago, one of the members spoke of the relationship between Majocchi's disease and Gougerot's disease and the fact that in certain patients it is difficult to differentiate between them. If there is such a thing as Majocchi's disease, I think that this is a typical example of it. This patient has annular purpuric lesions on the inner side of her thighs.

DR. H. H. JOHNSON: I should like to ask whether any one has tried rutin for this disease. It is known to decrease capillary hemorrhage in patients with hypertensive disease, and it apparently is a nontoxic drug. I think that it might be tried to see what results would be obtained.

DR. H. A. HAYNES JR.: I have seen a patient at Ann Arbor, Mich., who has Majocchi's disease. The purpuric lesions become tan for six or eight months, and then there is a recurrent stage of redness. The disease has been fluctuating for thirty years, without any more change than that.

Leukemic Infiltration in Scars of Herpes Zoster Generalisatus. Presented by DR. E. W. NETHERTON.

Mrs. G. B., a widow aged 55, is presented because of an eruption of about eight weeks' duration. She has been receiving treatment at the Cleveland Clinic since March 1944 for chronic lymphatic leukemia. In 1943 she had cerebrospinal meningitis; at this time the lymphatic leukemia was discovered. Her hemograms show white blood cell counts varying from 51,200 white cells per cubic millimeter to 10,350 per cubic millimeter. The differential count has shown a decided predominance of lymphocytes. The superficial lymph nodes have become enlarged, but they usually decrease in size following treatment with roentgen rays. About Aug. 26, 1946, severe herpes zoster developed, involving the upper portion of the back and the lateral and anterior surfaces of the right arm. The palm and the dorsal surface of the right hand were also involved. Nine days after the onset of the herpes zoster and at the height of the eruption, there were hemorrhagic vesicles and the pain was intense. Numerous varicelliform lesions appeared on the face, trunk and extremities. She stated that she has not had chickenpox and, as far as she knows, had not been exposed to chickenpox just prior to the onset of the herpes zoster. Within three weeks the vesicular phase of the herpes zoster, as well as the varicelliform eruption, had disappeared, leaving light red scars. The

pain in the right arm remained intense, and there was partial paralysis of the arm.

On October 4, it was noted that the erythematous scars of herpes zoster, as well as the remnant of the varicelliform eruption, were becoming infiltrated. The infiltration increased to the extent that the lesions became infiltrated papules and the larger scars of the herpes zoster were definitely infiltrated.

On September 3, the hemogram showed 22,100 white blood cells per cubic millimeter, with a differential count of 44 per cent neutrophils, 50 per cent lymphocytes, 0.5 per cent eosinophils and 3.5 per cent monocytes. Two per cent atypical large lymphocytes were present. On September 16, the white blood cell count was 14,350 and the differential count disclosed 19 per cent neutrophils, 80 per cent lymphocytes and 1 per cent eosinophils. Both of these counts were taken after roentgen rays had been given for a period of about two weeks.

On the upper right portion of the back there is a large area consisting of infiltrated papules, some of which have become confluent, forming an infiltrated plaque. On the outer and anterior surfaces of the right arm and on the dorsal and palmar surfaces of the hand, the herpes zoster scars are raised, dull red and infiltrated. Scattered over the face and body there are numerous match head-sized to split pea-sized light red infiltrated papules, some of which show central scarring, with thin adherent scaly crusts, which resulted from the varicelliform eruption.

Tissue was removed from the scar of herpes zoster and from a papular lesion at the site of a varicelliform lesion. The histologic changes in both were essentially the same. The epidermis was thin, and there was slight intracellular edema in the rete. Throughout the corium there were areas of dense cellular infiltration. In some areas the infiltrate consisted chiefly of lymphocytes, while in other foci there were large mononuclear cells with vesicular nuclei. Fibroblasts were numerous. There was an occasional multinucleated cell. There were no eosinophils, leukocytes or plasma cells.

A biopsy specimen was also obtained from an apparently normal portion of skin, and this showed no significant changes other than edema of the papillary layer of the corium.

In an effort to determine whether trauma of the skin would be followed by the development of an infiltrated papule, into one area 0.1 cc. of 1 per cent procaine hydrochloride was injected and another area was infiltrated with 0.5 cc. of the patient's own blood.

DISCUSSION

DR. H. J. PARKHURST (Toledo, Ohio): I think that the generalized forms of herpes zoster are rather likely to occur in patients with leukemia. This patient had had the disease two years before herpes zoster appeared. I was interested to see the infiltration in the scars of herpes zoster.

Amyloidosis Cutis of the Legs. Presented by DR. R. C. LIGHT, DR. J. KAM and DR. A. E. WALKER (service of DR. H. N. COLE and DR. J. R. DRIVER).

CORRECTION

In the Directory of Dermatologic Societies, under national societies, in the January issue (ARCH. DERMAT. & SYPH. **57**:136, 1948), the date of the meeting of the American Dermatological Association is given as May 17 to 20. The date has now been set as April 26 to 29, 1949.

In the article by Dr. Walter F. Lever, "Sebaceous Adenoma: Review of the Literature and Report of a Case," in the January issue ARCH. DERM. & SYPH., **57**:102, (1948), a line was accidentally dropped from the last paragraph on page 107. The third sentence in the paragraph should read: "The lobules on the right side of the tumor (fig. 3) showed preponderately generative and transitional cells, so that this part of the tumor resembles a sebaceous epithelioma. The lobules on the left side of the tumor (fig. 4) contained more sebaceous than generative cells, causing a resemblance of this part of the tumor to nevus sebaceus."